This Issue Exceeds 103,700 Copies

THE JOURNAL

OF THE

American Medical Association

Subscription, $8.00 | PUBLISHED WEEKLY | Single Copies, 25 Cents

VOLUME 117, No. 18

COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street, Chicago, Ill.

NOVEMBER 1, 1941

CONTENTS AND SUBJECT INDEX

The Diagnosis and Treatment of Mild Vitamin Deficiencies. Julian M. Ruffin, M.D., Durham, N. C.1493

Treatment of Neuropsychiatric Disorders with Vitamins. Norman Jolliffe, M.D., New York.....1496
Papers of Drs. Ruffin and Jolliffe discussed by Drs. Moersch, Wechsler, Mills, Zeligs, Schiff, Mackie and Jolliffe.

Thrombophlebitis and Pulmonary Embolism. Claude E. Welch, M.D., and Henry H. Faxon, M.D., Boston 1502
Discussed by Drs. Ochsner, Lam and Faxon.

The Surgical Treatment of Hypertension: II. Comparison of Mortality Following Operation with That of the Wagener-Keith Medically Treated Control Series. Ward Wilson Woods, M.D., and Max Minor Peet, M.D., Ann Arbor, Mich. 1508

Double Uterus with Pregnancy. Goodrich C. Schauffler, M.D., Portland, Ore. 1516
Discussed by Drs. Miller and Schauffler.

Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children. Merlin L. Cooper, M.D.; Ralph L. Zucker, M.D., and Stewart Wagoner, M.D., with statistical analyses by Mrs. Estelle W. Brown and Ruth Bennett, M.D., Cincinnati 1520

Alcohol and the Pedestrian in Traffic Accidents. Thomas A. Gonzales, M.D., and Alexander O. Gettler, Ph.D., New York.....1523

Production of Experimental Osteomyelitis. Louis Scheman, M.D.; Martha Janota, M.S., and Philip Lewin, M.D., Chicago.....1525

Treatment of Myasthenia Gravis by Removal of Thymus Gland. Alfred Blalock, M.D.; A. M. Harvey, M.D.; F. R. Ford, M.D., and J. L. Lilienthal Jr., M.D., Baltimore.1529

CLINICAL NOTES, SUGGESTIONS AND NEW INSTRUMENTS

Identification of the Organism of Subacute Endocarditis and Systemic Mycosis. S. H. Polayes, M.D., Brooklyn, and C. W. Emmons, Ph.D., Bethesda, Md. 1533

Paraldehyde Poisoning. Mervyn Shoor, M.D., San Francisco...1534

Plexiform Neurofibroma Invading the Oral Cavity. Hayes Martin, M.D., and Clifford L. Graves, M.D., New York 1535

COUNCIL ON PHARMACY AND CHEMISTRY 1539

EDITORIALS

Army Morale and the Medical Reserve Corps 1540

Air Borne Influenza Virus.....1541

CURRENT COMMENT

Cancer Mortality Declines in New York 1542

Weight Reduction Diets.....1542

Diet and Cirrhosis of the Liver 1542

BUREAU OF LEGAL MEDICINE AND LEGISLATION 1559

(Subject Index on next page)

MEDICAL PREPAREDNESS

New Navy Medical Center.....1543

New Navy Hospitals and Dispensaries 1543

Army Reserve Officers Ordered to Active Duty.....1545

ORGANIZATION SECTION 1547

A. M. A. SESSION ATLANTIC CITY JUNE 8-12, 1942

Military Medicine—Military Surgery

Because of the urgent demand for authoritative and up-to-date information on Military Medicine and Surgery, and with the desire to cooperate to the fullest with the National Defense Program, we announce here *Two* great Symposia that are of immediate importance to the entire medical profession —to doctors in civil practice as well as to those in the Service.

The *first* of these Two Symposia is on *Military Medicine* and appears in the *November* Number of the MEDICAL Clinics of North America. It is headed by Rear Admiral Ross T. McIntire, Surgeon General of the United States Navy.

The *second* Symposium is on *Military Surgery* and will appear in the *December* Number of the SURGICAL Clinics of North America. It is headed by Major General James C. Magee, Surgeon General of the United States Army.

These two Symposia have been specially designed to help you in the part you, as an individual, may be called upon to fulfill in the interest of National Defense. They are comprehensive, practical and deal specifically with *Today's* problems in Military Medicine and Surgery and have been written by leading Officers of the Army and Navy and by outstanding authorities in civil practice—selected by Surgeon Generals Magee and McIntire.

Each Symposium ideally complements the other. These are, therefore, excellent Numbers with which to begin your subscriptions to *both* the *Medical* Clinics of North America and the *Surgical* Clinics of North America. *Order Today!*

See Contents in SAUNDERS Advertisement—Pages 3, 4, 5

SUBJECT INDEX TO THIS ISSUE

The letters used to explain in which department the matter indexed appears are as follows: The Star (*) indicates an Original Article; "ab," abstract; "E," Editorial; "C," Correspondence; "MI," Medicolegal; "ME," Medical Economics; "OS," Organization Section; "SS," Student Section.

A. M. A. exhibits from headquarters..OS-1547
Academy of Medicine, Atlanta, new home..1548
Accidents, traffic, alcohol and pedestrian..*1523
Acid, nicotinic, deficiency.....*1496
nicotinic, foods rich in.....*1495
Air borne influenza virus.....E-1541
Alcohol in brain, spinal fluid; determination.*1524
Alcoholism, pedestrian in traffic accidents.*1523
Allergy, cold, due to ice-bag.....1576
nasal, in children.....ab-1572
thiamine hydrochloride ab-1501
Aluminum subacetate for senile eczema....1576
American College of Surgeons.....1550
Conference on Industrial Health.....1551
Rheumatism Association proceedings....1560
Amino acids in diet and liver cirrhosis..E-1542
Anemia, pernicious, vitamin B_1 in funicular myelosis ab-1572
Anesthesia, paraldehyde rectally, fatal poisoning from *1534
Armstrong, Charles, Sedgwick Medal to....1550
Army morale E-1540
Arthritis, American Rheumatism Association proceedings 1560
gold therapy.....ab-1560; ab-1561; ab-1562
Asthma, whooping cough vaccine cause?....1576
Automobile, alcohol and pedestrian.....*1523
Aviation, pilot's capacity; pressure cabin in planes ab-1570
Bailleul, L. C., death.....1551
Barium sulfate, aspiration into trachea.....1576
Barnard Hospital Lecture, Dr. Murphy to deliver 1549
Bismuth injection in peanut oil, urticaria after 1576
Bladder calculi, lead and silver in.....C-1557
Blood alcohol, determination.....*1524
plasma bank by American Red Cross....1544
pressure, high experimental.....ab-1567
pressure, high, surgical treatment.....*1508
Board Examinations 1558
Body, weight, inability to gain.....1575
weight reduction diets.....E-1542
Bones, polyostotic fibrous dysplasia.....ab-1567
Book Notices 1573
Books Received.....Adv. page 32
Brain alcohol, determination.....*1524
British Emergency Medical Services.....1552
Brucellosis ab-1568
Bureau of Investigation.....1556
Bureau of Legal Medicine and Legislation.1559
Calcaneus, healed defect in, after osteomyelitis 1576
Calcium aurothiomalate in arthritis.....ab-1561; ab-1565
Calculi, lead and silver in.....C-1557
Cancer mortality declines in New York..E-1542
Candida parakrusei cause of endocarditis.*1533
Carotene, toxicity 1575
Central Society for Clinical Research.....1550
Cerebrospinal Fluid, alcohol in.....*1524
Children's health, improved by migration to country, England 1553
Clinical Research, Central Society for.....1550
Cold allergy due to ice-bag.....1576
Correspondence 1557
Council on Pharmacy and Chemistry.....1539
Czerny, Adalbert, death.....1551
Deaths 1554
Diarrhea, acute, sulfathiazole for.....*1520
Diet and liver cirrhosis.....E-1542
weight reduction E-1542
Diphtheria, active immunization.....ab-1572
Diuresis, antidiuretic, in eclamptic.....C-1557
Dysentery, acute, sulfathiazole for.....*1520
Dystrophy, muscular, vitamins for.....*1498
Eclampsia: antidiuretic principle.....C-1557
Eczema, senile, treatment.....1576
Edema, angioneurotic 1575
Embolism, pulmonary, and thrombophlebitis.*1502
Encephalopathy, nicotinic acid deficiency..*1496
Endocarditis, subacute, Monilia parakrusei cause of *1533
European War, bombing London University.1552
children's health improved.....1553
effect on medical libraries.....1552
Emergency Medical Services.....1552
health of troops in Middle East.....1553
venereal diseases and.....1552
Eyes, paralysis, Wernicke's, vitamins for..*1498
Face, plexiform neurofibroma.....*1535
Foods rich in vitamins.....*1495
Foreign Letters 1552
Fulton County Medical Society, new home..1548
Ganglionectomy in hypertension.....*1508
Goiter, Exophthalmic, pathogenesis.....ab-1571
Gold metabolism ab-1561
therapy in arthritis.ab-1560; ab-1561; ab-1562
Government Services 1551
Headgear: Army cold weather.....1544
Health of county society members.....1550
study of private agencies.....1551
U. S. P. H. S. districts reorganized.....1551
Heat loss of body, effects of wind on.....1544
"Hollywood" reducing diets.....E-1542
Hooper Foundation, poliomyelitis survey...1550
Hospitals, county hospital; operation a governmental function MI-1559
Hyperthyroidism and adenocarcinoma...ab-1568
Ice-bag, cold allergy due to.....1576
Industrial Health, American Conference on.1551
Influenza virus, air borne.....E-1541
Interns from Latin America.....1551
Jaundice, Weil's disease, mouse protection test ab-1570
Koch, Fred C., professor emeritus.....1548
Korsakoff Syndrome, vitamins for.....*1498
Labor, fatal, paraldehyde poisoning.....*1534
Lead in urinary calculi C-1557
Lectures, public, New York.....1550
Libraries, medical, European War detrimental to 1552
Liver, alcohol in, vs. fatal accidents to pedestrians *1524
cirrhosis of, and diet.....E-1542
Marching and vitamin C.....ab-1572
Marriages 1553
Mayo Lectures on civilian and military practice 1549
Medical Education, annual clinic, Mich.....1549
graduate institute, Rochester.....1549
graduate programs, Ia.....1548
Medical Examinations and Licensure.....1558
Medical Institute in Toledo.....1550
Medical Preparedness 1543
American Red Cross to teach home nursing 1544
Army cold weather headgear.....1544
Army morale E-1540
blood plasma bank.....1544
Mayo lectures 1549
Medical Reserve Corps officers, promotion E-1540
Navy hospitals and dispensaries.....1543
Navy Medical Center.....1543
Navy medical corps appointments, examinations for 1543
officers ordered to active duty.....1545
sparkproof shoes for armored troops.....1544
Medicolegal Abstracts 1559
Meetings, Coming Meetings.....1560
Milk, raw, brucellosis from.....ab-1568
Monilia, parakrusei, endocarditis from....*1533
Motorcycles, alcohol and pedestrian in accidents *1523
Mouth, plexiform neurofibroma.....*1535
Murphy, James B., Barnard Hospital Lecture by 1549
Muscles, pain from marching, vitamin C for ab-1572
Myasthenia gravis, thymectomy for.....*1529
Mycosis, systemic, from Candida parakrusei *1533
Myocrysin ab-1561
National Health Council to study private health agencies 1551
Nephrectomy and hypertension.....ab-1567
Nerves, splanchnicectomy in hypertension..*1508
Neurasthenia, vitamin therapy.....*1498
Neurofibroma, plexiform of oral cavity...*1535
Neuropsychiatry disorders, vitamins treatment *1496
Nevus, unilateral ab-1568
New and Nonofficial Remedies.....1539
New York, cancer mortality declines in..E-1542
News 1548
Nose, allergy in children.....ab-1572
Nursing, home, Red Cross to teach.....1544
Obesity, weight reduction diets.....E-1542
Old Age, eczema in, treatment.....1576
Organization Section 1547
Osteomyelitis, healed defect in os calcis after.1576
produced by sodium morrhuate and staphylococcus *1525
Pancreatitis, acute, with mumps.....ab-1572
Paraldehyde by rectum, fatal poisoning...*1534
Paralysis agitans, vitamins therapy.....*1498
Parotitis, acute pancreatitis with.....ab-1572
convalescent serum to treat whooping cough ab-1572
Peanut Oil, urticaria from bismuth injected in 1576
Pedestrian and alcohol.....*1523
Pellagra: early subclinical deficiencies....*1494
psychosis, vitamins for.....*1498
Philadelphia County Medical Society.....1550
Phlebitis *1503
Phlebothrombosis *1502
Physicians ordered to active duty.....1545
Philadelphia County Society studies health of 1550
Pituitary activity, antidiuretic principle..C-1557
Poliomyelitis, convalescent serum for....ab-1569
survey by Hooper Foundation.....1550
vitamins for *1498
Polyostotic fibrous dysplasia.....ab-1567
Pregnancy, double uterus with.....*1516
Prizes, Bigelow Medal.....1549
Sedgwick Medal 1550
Protein poor ration and liver cirrhosis...E-1542
Psychosis, vitamin treatment.....*1496
Queries and Miner Notes.....1575
von Recklinghausen's disease, invading oral cavity *1535
Red Cross, blood plasma bank.....1544
to teach home nursing.....1544
Rheumatism, American Rheumatism Association proceedings 1560
Riboflavin, foods rich in.....*1495
Sclerosis, amyotrophic lateral, vitamins for.*1498
Shoes, sparkproof, for armored troops.....1544
Silver in urinary calculi.....C-1557
Society Proceedings 1560
Sodium morrhuate, osteomyelitis produced by *1525
Soldiers and vitamin C.....ab-1572
Southern Medical Association.....1551
Spencer, Herbert Ritchie, death.....1551
Spinal Cord, vitamin B_1 in funicular myelosis ab-1572
Staphylococcus aureus, osteomyelitis produced by *1525
State Board Examinations.....1558
Stomach, chronic gastritis.....ab-1569
Streptococcus influenzal infection.....E-1541
Subways accidents and alcohol.....*1523
Sulfathiazole for acute diarrhea and dysentery *1520
Sullivan County Society lectures, N. Y.....1549
Surgeons, American College of, meeting...1550
Syphilis in Rio de Janeiro.....1553
Temperatures, high and low, vs. vitamin requirements ab-1500
Thiamine hydrochloride solution, hypersensitivity ab-1501
overdosage and toxicity.....ab-1500; 1575
subclinical deficiencies *1494
Thrombophlebitis and pulmonary embolism.*1502
Thymectomy for myasthenia gravis.....*1529
Thyroid, adenocarcinoma ab-1568
Tonics and Sedatives.....Adv. page 28
Trachea, barium sulfate aspirated into.....1576
Tropics, vitamin requirements in.....ab-1500
Tuberculosis case-finding study, N. Y.....1549
Typhus, epidemic, immunization.....ab-1571
University of London, bombing on.....1552
of Michigan, Dr. Vaughan dean.....1549
Ureters calculi, lead and silver in.....C-1557
Urticaria after injecting bismuth in peanut oil 1576
obscure 1575
Uterus, double, with pregnancy.....*1516
Varicose Veins, high ligation in.....C-1557
Vaughan, Henry F., named dean.....1549
Venereal Diseases and European War.....1552
Vitamin B_1 in funicular myelosis.....ab-1572
B_1, toxicity of.....1575
C and marching.....ab-1572
C, toxicity of.....1575
D, toxicity of.....1575
deficiencies, mild *1493
foods rich in.....*1495
recommended dosage *1495
requirements, optimal, at high and low temperatures ab-1500
toxicity of.....ab-1500; ab-1501; 1575
treatment of neuropsychiatric disorders.*1496
Voiceless patients, clinic to help.....1549
Wernicke's ophthalmoplegia, vitamins for.*1498
Whipple, A. O., Bigelow Medal to.....1549
Whooping Cough, convalescents serum from parotitis for ab-1572
vaccine cause of asthma?.....1576
Wind, effects on heat loss of body.....1544
Woman's Auxiliary 1547

THE JOURNAL of the American Medical Association is published weekly by the American Medical Association, 535 North Dearborn Street, Chicago, Ill. Subscription price, $8.00 a year. 25c a copy. Canadian $9.50. Foreign $12.00. Entered as second class matter June 25, 1885, at the Postoffice at Chicago, Ill., under Act of March 3, 1879.

ICHTHYOL* COUNCIL ACCEPTED

Prescribed for more than 50 years because of its mildly local antiseptic, astringent, and emollient properties. "Ichthyol" is the registered trade mark of the product supplied under the Merck label and originally introduced by Unna. Literature on request.

* The Merck Brand of Ichthammol, N. F.

MERCK & CO. INC.
Manufacturing Chemists
RAHWAY, N. J.

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 117, NO. 18 — COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION — CHICAGO, ILLINOIS — NOVEMBER 1, 1941

THE DIAGNOSIS AND TREATMENT OF MILD VITAMIN DEFICIENCIES

A CLINICAL DISCUSSION

JULIAN M. RUFFIN, M.D.

Associate Professor of Medicine, Duke University School of Medicine

DURHAM, N. C.

The recognition of a full blown vitamin deficiency such as acute pellagra, beriberi with peripheral neuritis, ariboflavinosis, scurvy and rickets is relatively simple. The characteristic dermatitis, the appearance of the gums, mouth and tongue, the cheilosis, the keratitis, the mental confusion or delirium, the diarrhea and the paresthesias of the extremities constitute a picture familiar to all and need no elaboration. It is now generally accepted that an easily recognizable clinical picture results from an advanced deficiency of the following vitamins: A, B_1 (thiamine hydrochloride), nicotinic acid, riboflavin, C (ascorbic acid), D and K.[1] While a number of other vitamins have been identified, there is still some doubt that their deficiency produces a characteristic syndrome in man.

In recent years many excellent communications[2] dealing with deficiencies of the B complex have appeared. It has been shown also by numerous observers that single vitamin deficiencies rarely if ever occur, a fact generally accepted today and one which should be borne in mind constantly when the question of treatment is being considered.

It is reasonable to assume that all grades of deficiencies exist, ranging from those which are totally unrecognizable in the light of our present knowledge to those presenting the characteristic features that have just been mentioned.

It is highly probable that for every patient having an advanced vitamin deficiency there are many patients having a subclinical or mild deficiency state. It is with this group that my concern lies at the present time.

DIAGNOSIS

While the diagnosis of advanced deficiency states usually is easy, the recognition of the mild or early vitamin deficiency is much more difficult. The diagnosis would obviously depend on a correct evaluation of the symptoms, signs and accessory findings in any given case, and also on the response to specific therapy. It must be pointed out, however, that improvement after vitamin therapy in such symptoms as flatulence, indigestion, weakness, nervousness and irritability does not necessarily constitute proof of a deficiency state, as the same improvement frequently is encountered when a patient having these symptoms is treated with such drugs as phenobarbital and belladonna. Improvement in such a vague clinical picture should be construed only as suggestive evidence of a state of subclinical deficiency.

Naturally the history of subsistence on a grossly inadequate diet would lead one to suspect the presence of an early vitamin deficiency, and it must be admitted that, in spite of an intensive educational program, the diet of the average tenant farmer of the South during the late fall, winter and early spring months is still definitely deficient, generally consisting of white bread, corn bread, hominy grits, potatoes (usually fried), fat back and other pork products, cow peas and molasses. Idiosyncrasies of diet, food faddism and ill balanced reducing diets also may lead to deficiency states.

SYMPTOMS

Among the early symptoms of vitamin deficiencies are anorexia with ensuing loss of weight, weakness, lassitude and easy fatigability, insomnia, increased nervousness and irritability, headache, palpitation, precordial distress, vague gastrointestinal disturbances such as flatulence, indigestion, constipation or mild diarrhea, nausea and indefinite abdominal pain. The patient usually just does not feel well without being able to state exactly what is wrong. One realizes at once that the symptoms of the so-called gastric neuroses, psychoneuroses and neurasthenias are essentially those mentioned. While it is entirely possible that these conditions are in reality expressions of an early avitaminosis,

From the Department of Medicine, Duke University School of Medicine.

Read before the Section on Pharmacology and Therapeutics at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

1. Mackie, T. T.; Eddy, W. H., and Mills, M. A.: Vitamin Deficiencies in Gastrointestinal Disease, Ann. Int. Med. **14**: 28-41 (July) 1940.

2. These include:

Sydenstricker, V. P.: The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), Ann. Int. Med. **14**: 1499 (March) 1941.

Spies, T. D., and Cooper, Clark: Vitamin Deficiency, The Diagnosis of Pellagra, Internat. Clin. **4**: 1-11 (Dec.) 1937.

Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man: A Preliminary Note, Pub. Health Rep. **53**: 2282 (Dec. 30) 1938.

Jolliffe, Norman; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy, J. A. M. A. **114**: 307-312 (Jan. 27) 1940.

Jolliffe, Norman: The Diagnosis, Treatment and Prevention of B_1 Deficiency, Bull. New York Acad. Med. **15**: 469 (July) 1939.

Matthews, R. S.: Pellagra and Nicotinic Acid, J. A. M. A. **111**: 1148 (Sept. 24) 1938.

Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H., and Cleckley, H. M.: The Ocular Manifestations of Ariboflavinosis, Pub. Health. Rep. **55**: 157-169 (Jan. 26) 1940.

still in the present state of our knowledge it must be admitted that such a relationship is often difficult, if not impossible, to prove.

It is also difficult to determine whether these early symptoms are due to a deficiency of one particular vitamin or to a combination of them. For example, the symptoms of subclinical pellagra, of spontaneous and induced thiamine and of B_6 (pyridoxine) deficiencies listed in four different communications [3] are practically identical (table 1). From such a description, obviously it is impossible to identify an early nicotinic acid, a B_1 or a B_6 deficiency. The answer, of course, lies in the fact that single deficiencies rarely if ever occur spontaneously, and the syndrome referred to by these authors is in all probability that of an early mixed deficiency. One should take the position that patients presenting such symptoms should be suspected of having an early unspecified and probably mixed deficiency, but a definite diagnosis should be made only after more positive evidence has been obtained.

TABLE 1.—*Symptoms of Early Subclinical Deficiencies According to Other Authors (in Order Listed)*

Pellagra [3a]	Spontaneous Thiamine Deficiency [3b]	Induced Thiamine Deficiency [3c]	Vitamin B_6 Deficiency [3d]
Fatigue	Fatigue	Depressed mental states	Extreme nervousness
Insomnia	Anorexia	Generalized weakness	Insomnia
Anorexia	Insomnia	Dizziness	Irritability
Vertigo	Irritability	Backache	Abdominal pain
Paresthesia	"Gas"	Soreness of muscles	Weakness
Palpitation	Nausea	Palpitation	Difficulty in walking
Nervousness	Constipation	Dyspnea	
Headache	Discomfort in abdomen	Precordial distress	
Forgetfulness	Depression	Insomnia	
Apprehension	Backache	Anorexia	
Distractibility	Headache	Nausea	
	Sighing	Vomiting	
	Palpitation	Loss of weight	
	Precordial distress	Atony of muscles	

MANIFESTATIONS NECESSARY FOR DIAGNOSIS

It has been stated that advanced deficiencies of vitamins A, B_1, nicotinic acid, riboflavin and vitamins C, D and K result in easily recognizable clinical pictures and that the earliest symptoms of these deficiencies are so vague and indefinite as to render accurate classification impossible. However, at some stage in the development of a deficiency state there must come a time when certain conditions are present which will justify the diagnosis. The significant symptoms, signs and laboratory findings that are necessary for the recognition of various mild vitamin deficiencies are shown in table 2.

Most of the laboratory procedures mentioned require special apparatus and well trained technicians. The determinations of the blood level of vitamin C and the prothrombin time can be carried out in any well equipped laboratory, but the demonstration of a vitamin A, a nicotinic acid, a vitamin B_1 or a riboflavin deficiency by laboratory procedures lies at the present time in the province of the special investigator. So far as the general practitioner is concerned, the diagnosis will depend largely on a proper evaluation of the symptoms and signs as here described and their response to specific therapy.

TREATMENT

Dietary Treatment.—Theoretically, the treatment of the mild vitamin deficiencies is simple and may be described in a few words: a well balanced diet to which may be added such vitamins as are indicated in the individual case. The patient should be urged to eat a variety of meats, green vegetables, milk, eggs and fruit juices. If such a diet is followed, and if there is no underlying disease which interferes with proper absorption and utilization, recovery is the rule.

Unfortunately, it is one thing to prescribe a diet, but having the patient follow it is quite another matter. There are few of us who are willing to change the habits of a life time. This is particularly true of tenant farmers, most of whom were raised on a deficient diet and show no inclination to change it even though they are warned that its continuance may prove detrimental to their health. The economic factor likewise plays a large part. The deficient diet to which these people are accustomed is much cheaper than a well balanced one, and many of these patients simply cannot afford to buy the articles of food that they need. Foods rich in the various vitamins are shown in table 3.[4]

TABLE 2.—*Symptoms, Signs and Laboratory Findings Necessary for Diagnosis of Mild Vitamin Deficiencies* *

Vitamin Deficiency	Symptoms and Signs	Significant Laboratory Findings
A	Night blindness, scaly skin ?, hyperkeratosis	Decrease in blood level of vitamin A; adaptometer test (doubtful value unless visual threshold improves after administration of A) Stevens, D., and Wald, G.: J. Nutrition **21**: 461 (May) 1941
B_1	Paresthesia of extremities, muscle tenderness, impairment of vibratory sense, decreased tendon reflexes	Decrease in urinary excretion of thiamine (blood level remains about same)
Nicotinic acid	Sore mouth and tongue, redness of tongue margins and papillary atrophy, diarrhea, roughening, redness and scaliness of dorsum of hands, increased pigmentation over bony prominences	Decrease in urinary excretion of nicotinic acid derivatives (blood level remains about same)
Riboflavin	Photophobia and lacrimation, cheilosis, sore tongue with purplish color	Vascularization of cornea (slit lamp examination)
C	Irritability, spongy, bleeding gums, bone and joint pain, petechial hemorrhages (occur in other conditions also), bleeding	Lowering of vitamin C in plasma
D	Muscle weakness, head sweats	Low blood phosphorus, elevation of serum phosphatase ?, roentgen changes
K	Bleeding	Increased prothrombin time

* Modification of table by Mackie.[1]

Vitamin Therapy.—When specific and recognizable deficiencies are found, vitamin therapy is definitely indicated but should always supplement the dietary treat-

3. (*a*) Spies, T. D.; Aring, C. D.; Gelperin, Jules, and Bean, W. B.: The Mental Symptoms of Pellagra, Their Relief with Nicotinic Acid, Am. J. M. Sc. **196**: 461 (Oct.) 1938. (*b*) Jolliffe, Norman: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism, Quart. J. Stud. on Alcohol **1**: 517 (Dec.) 1940. (*c*) Williams, R. R.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B_1) Deficiency in Man, Arch. Int. Med. **66**: 785-799 (Oct.) 1940. (*d*) Spies, T. D.; Bean, W. B., and Ashe, W. F.: A Note on the Use of Vitamin B_6 in Human Nutrition, J. A. M. A. **112**: 2414-2415 (June 10) 1939.

4. (*a*) Sherman, H. C., and Lanford, C. S.: Essentials of Nutrition, New York, Macmillan Company, 1940, table 27, p. 371. (*b*) Bacharach, A. L.: The Distribution of Nicotinic Acid in Human and Animal Foods, Nutrition Abstr. & Rev. **10**: 459, 1941.

ment, never replace it. In our experience, when one is reasonably sure that a specific deficiency is present, the best results are obtained only if the patient is given adequate doses of the vitamin or vitamins in which he is lacking. In deficiencies of the water soluble vitamins, if no improvement is noted after ten to fourteen days of treatment, it is improbable that continued

TABLE 3.—*Foods Rich in Vitamins (According to Sherman and Lanford [4a])*

A	B_1	Nicotinic Acid [4b]	Riboflavin	C
Greens	Yeast	Liver	Brewers' yeast	Green peppers
Spinach	Wheat germ	Brewers' yeast	Liver	Broccoli
Kale	Ham	Beef	Kidney	Kale
Turnips	Pork	Salmon	Cheese	Turnip greens
Collards	Liver	Peanuts	Eggs	Collards
Liver	Kidney	Whole wheat bread	Ham	Cauliflower
Butter	Eggs	Soy beans	Spinach	Lemons
Cheese	Nuts	Spinach	Beef	Oranges
Carrots	Green peas	Lamb	Milk	Grapefruit
Broccoli	Lima beans	Tongue	Broccoli	Cabbage
Eggs	Shad roe	Shad roe	Collards	Tomatoes
Squash	Corn meal	Green peppers	Peas	Strawberry

Vitamin K is present in almost all green vegetables.

therapy will prove of value, and certainly there is little justification for continuing it longer than from three to four weeks. With the fat soluble vitamin deficiencies, however, especially vitamin A, it may be necessary to continue treatment for a longer period of time. The most outstanding feature of the treatment of acute and severe vitamin deficiencies is the remarkable rapidity with which symptoms subside when specific deficiencies are corrected by the administration of specific vitamins. It is justifiable to assume that in the mild deficiencies improvement should be noted just as rapidly as in the severe ones, and failure of the patient to improve after a reasonable length of time means either that there is a mistaken diagnosis or that irreversible changes have taken place. In such cases further vitamin therapy is futile.

In certain instances, the parenteral administration of vitamins is not only justified but definitely indicated. In the preparation of the patient for an abdominal operation it is customary to administer large quantities of dextrose and saline solution by vein or subcutaneously.

It has been emphasized by several writers that such a procedure may precipitate an acute deficiency state which might prove serious if not recognized and corrected. It is wise, therefore, whenever a subclinical deficiency is suspected, to give these patients, along with their dextrose, nicotinic acid, thiamine hydrochloride, riboflavin and ascorbic acid as a part of the preoperative care. In fact, the question of gastrointestinal absorption of vitamins is so poorly understood at the present time that one is justified in administering certain of the vitamins parenterally when specific deficiencies are suspected. This is particularly true in vitamin B_1 and nicotinic acid deficiencies. It is customary to give 100 to 200 mg. of nicotinic acid and 20 to 30 mg. of thiamine hydrochloride intravenously for from three to five days even though the deficiency is mild, continuing with the oral administration in much smaller doses for two to three weeks. The dosage recommended, after an initial three to five day period in which larger doses are used either by mouth or parenterally, is shown in table 4.

The fact that single deficiencies are rarely, if ever, encountered is an excellent argument against the treatment of deficiency states with chemically pure substances. There are probably other vitamins as yet unknown which are essential to health. It is generally believed that yeast and whole liver contain most of the vitamins of the B complex, and it is a good practice when the patient can afford it to give whole liver, or an extract of liver, either by mouth or intramuscularly. If liver extract cannot be obtained, brewers' yeast or autolyzed yeast (vegex) is a satisfactory substitute. This point is well illustrated by the following case.

REPORT OF CASE

J. H. D., a white man aged 26, admitted to Duke Hospital Feb. 5, 1940, complained of loss of weight, diarrhea, weakness, sore tongue and tingling and numbness of the extremities of six months' duration. On examination he was emaciated but mentally alert. There were fissures at the corners of the mouth. The tongue was beefy red with papillary atrophy. There was some redness of the dorsum of the hands and considerable roughening and scaliness of the skin over the body, with enlargement of the hair follicles.

The significant accessory findings were a macrocytic anemia, a hemoglobin content of 13.2 Gm. and a red blood cell count of 2,400,000; there was no free acid after histamine; the dextrose tolerance curve was flat and stool fat was 38 per cent. The ascorbic acid content of the blood was too low to be measured, being less than 0.1 mg. per hundred cubic centimeters of plasma.

A diagnosis of multiple vitamin deficiencies was made, including sprue, pellagra, scurvy and either a riboflavin or a pyridoxine deficiency. He was given pyridoxine 50 mg. daily intravenously for ten days, with no appreciable improvement. Large intravenous doses of nicotinic acid, of riboflavin and of ascorbic acid failed to produce any effect. However, Lederle's liver extract 3 cc. daily was followed by rapid improvement and eventually complete recovery.

One must not lose sight of the fact that many maladjusted and neurasthenic persons have a coexisting mild vitamin deficiency. It is important, of course, to correct this deficiency by diet if possible, supplemented by vitamins if necessary. It is equally important to realize that vitamins are not the panacea of all ills;

TABLE 4.—*Recommended Dosage of Vitamins in Treatment of Mild Deficiencies*

Vitamin	Dosage (Oral)
A	15,000-20,000 U. S. P. units a day
Thiamine hydrochloride	5 mg. three times a day
Nicotinic acid	50 mg. three times a day
Riboflavin	1 mg. three times a day
Ascorbic acid	0.1 Gm. three times a day
D	2,000-2,500 U. S. P. units a day
K	1 mg. daily

that they afford little relief in social, financial or domestic problems; that long continued treatment with expensive vitamins is a serious and unnecessary drain on the patient's pocketbook and that, in the last analysis, a well balanced diet is the best treatment in most of the cases of mild vitamin deficiencies.

COMMENT

My purpose in this communication is to call attention to the fact that while vitamin deficiencies constitute an extremely important group of diseases, the trend of recent events leads one to feel that both the public and the medical profession have become overenthusiastic on

the subject of vitamins. There is a rapidly growing tendency today to attribute most of the ills of the human race to a deficiency of this or that vitamin. The suggestion is being made that the neurotic, the neurasthenic, the mentally retarded, the biologically unfit or constitutional inferiority are often expressions of deficiency states. This may or may not be true; certainly it is extremely difficult to prove any causal relationship. It is entirely possible that many of them are the result of subclinical deficiency states existing since birth. If this is true it is highly probable that, in the adult at least, irreversible intracellular changes have taken place and vitamin therapy even over a prolonged period of time will be of little value. They should not be denied the benefit of vitamin therapy, but it is much more important to prescribe an adequate diet than to allow the patient to continue eating a restricted one and hope to make up for its deficiencies by the addition of various vitamins. It should be emphasized also that when specific deficiencies occur the response to specific therapy is unusually rapid and dramatic, and if the patient shows no improvement after three or four weeks there is little justification in allowing him to continue to buy drugs, especially those containing the B complex, which in all probability will benefit only the manufacturer. Contrary to the report of others,[5] my experiences in the treatment of patients suspected of having a mild deficiency with the known members of the B complex have been disappointing. It is true that many will report temporary improvement, but this hardly justifies the conclusion that the vitamins that were given to the patient were responsible for this improvement, for the factor of psychotherapy has to be taken into consideration. If conditions at home are bad, if the patient is overworked and underfed as many of our clinic patients are, if financial worries or domestic unhappiness weigh heavily on him, usually he returns six months or a year later with the same or new complaints. There is little to justify long-continued vitamin therapy in a patient whose domestic life is such as to make health and happiness difficult if not impossible to attain. For example, the farmwife who at the age of 30 has borne six children, who does all the housework including the cooking, washing and ironing and then works in the fields during the day can expect little relief from her weakness, nervousness, headache, fatigability, low back pain, abdominal distress and vague digestive disturbances by the administration of vitamins. What she obviously needs is not vitamins but rest, a well balanced diet and a complete change in her daily routine. She represents what may be called a social and economic rather than a medical problem.

When a mild vitamin deficiency is recognized, or even suspected, certainly therapy should be instituted at once, but it must be remembered that by far the best treatment is an adequate diet, specific vitamins being used only as supplementary therapy. The solution of the problem of the deficiency diseases lies not so much in the cure of the deficiency as in its prevention, not in the administration of pills but in an educational and social program which will not only teach the poorer classes what to eat but make it possible for them to secure the articles of food which are necessary for the maintenance of health.

5. Spies, T. D.; Swain, A. P., and Grant, J. M.: Clinically Associated Deficiency Diseases, Am. J. M. Sc. **200**: 536 (Oct.) 1940.

TREATMENT OF NEUROPSYCHIATRIC DISORDERS WITH VITAMINS

NORMAN JOLLIFFE, M.D.
NEW YORK

During the past decade vitamin deficiency has been looked for and often found in many neuropsychiatric disorders. It must be emphasized, however, that merely finding a vitamin deficiency concurrent with a disease does not indicate that this deficiency is the cause of the original disease. Secondary or "conditioned" vitamin deficiencies should be clearly distinguished from the original or primary disease, else utter confusion will result.

Almost every vitamin has also been credited with playing a role in the maintenance of a normal nervous system. The more important of the vitamins thus accredited are thiamine hydrochloride, nicotinic acid, riboflavin, pyridoxine and alpha-tocopherol. Only thiamine hydrochloride and nicotinic acid, however, have been related clinically in a definite causal role to neuropsychiatric syndromes in man.

The sequence of events in a vitamin deficiency disease begins with an inadequate vitamin supply, due to failure to ingest, absorb or utilize, followed in succession by tissue depletion, biochemical "lesions," [1] reversible anatomic changes and finally irreversible anatomic lesions. Adequate treatment initiates the sequence of tissue replenishment, early disappearance of the biochemical "lesions" and less rapid disappearance of the reversible anatomic lesions. The importance of early diagnosis and treatment is obvious.

The neuropsychiatric conditions in which there is substantial evidence that a vitamin deficiency may play an etiologic role are listed in table 1. This table includes the vitamin or vitamins predominantly concerned, an evaluation of vitamin therapy and references to the literature for each of the conditions listed. The evaluation of therapy concerns only the primary disease and is made without prejudice to the value of vitamins in the prevention or treatment of a secondary deficiency. This table does not include a number of neuropsychiatric syndromes, such as sciatica, eighth nerve deafness and other single nerve neuropathies, herpes zoster, hysteria, impotence and psychogenic pain, for which vitamins have been recommended because of their drug action or for use as a placebo, in which conditions the rationale of their use is dubious or the results claimed can be explained equally well or better as fortuitous.

A neurasthenic syndrome is probably the earliest and most frequent manifestation of both thiamine deficiency [2]

From the Medical Service of the Psychiatric Division, Bellevue Hospital, and the Department of Medicine, New York University College of Medicine.

Read before the Section on Pharmacology and Therapeutics at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 4, 1941.

Studies on which this paper is based were aided by grants from the John and Mary R. Markle Foundation, the Dazian Foundation for Medical Research, the Williams-Waterman Fund of the Research Corporation and the Nutritional Research Fund of the Medical Service of the Psychiatric Division of Bellevue Hospital.

1. Peters, R. A.: The Biochemical Lesion in Vitamin B_1 Deficiencies, Lancet **1**: 1161 (May 23) 1936.

2. Williams, R. D.; Mason, H. L., and Smith, B. F.: Induced Vitamin B_1 Deficiency in Human Subjects, Proc. Staff Meet., Mayo Clin. **14**: 787 (Dec. 13) 1939. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B_1) Deficiency in Man, Arch. Int. Med. **66**: 785 (Oct.) 1940. Jolliffe, Norman; Goodhart, Robert; Gennis, J., and Cline, J. K.: The Experimental Production of Vitamin B_1 Deficiency in Normal Subjects: The Dependence of the Urinary Excretion of Thiamine on the Dietary Intake of Vitamin B_1, Am. J. M. Sc. **198**: 198 (Aug.) 1939. Jolliffe, Norman: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: Part I, Quart. J. Stud. on Alcohol **1**: 517 (Dec.) 1940. Recent Advances in Clinical Applications of the B Vitamins, J. Am. Diet. A. **17**: 5 (Jan.) 1941; Newer Knowledge of the Vitamin B Complex, Bull. New York Acad. Med. **17**: 195 (March) 1941.

and pellagra.[3] As in neurasthenic syndromes of any origin, the symptomatology is varied but the outstanding characteristics are anorexia, fatigue and insomnia. It should not be inferred that all neurasthenia is based on vitamin deficiency. Such is definitely not the case.

The polyneuropathies of thiamine deficiency,[4] whether mild or severe, are bilateral and symmetrical and characteristically involve first and predominantly the lower extremities. Peripheral neuropathy that involves a single nerve, that is not bilateral and symmetrical or that does not involve first and predominantly the lower extremities is not, in my experience, due to thiamine deficiency alone. The polyneuropathies fulfilling the foregoing criteria occurring in association with beriberi, alcoholism, pellagra, pregnancy, cachexia, diabetes, hyperthyroidism and chronic diarrheal diseases are usually a manifestation of thiamine deficiency. There is often coexisting latent or manifest deficiency of other vitamins.

Wernicke's disease[5] occurs most often, but not exclusively, in association with chronic alcoholism. It is characterized clinically by ophthalmoplegia, polyneuropathy, ataxia and progressive clouding of consciousness. It is usually associated with multiple vitamin deficiencies. Thiamine, when administered in adequate amounts, relieves the ophthalmoplegia within forty-eight to ninety-six hours.[6] The mental status is frequently but not consistently improved by thiamine therapy.

The mental symptoms most commonly seen in pellagra[7] are those usually seen in any organic psychosis. These include memory defects, disorientation, confusion and confabulation. Periods of excitement, depression, mania, delirium and paranoia occur not infrequently. These cerebral disorders may appear before other signs of pellagra are evident. Response to nicotinic acid is usually prompt, especially when the psychosis is of short duration. In the psychoses of longer duration the response is by no means spectacular, and frequently specific therapy does not help at all. This means that in the latter cases the processes may have advanced to the irreversible anatomic stage. It must be emphasized, however, that pellagrins lack other dietary factors necessary for normal brain metabolism, and these deficiencies may contribute to the cerebral manifestations. Adequate amounts of all other nutritive essentials should therefore be given in order to obtain a maximal therapeutic response.

Nicotinic acid deficiency encephalopathy is a term used by us[8] to designate a syndrome characterized by sucking and grasping reflexes, changing cogwheel rigidities and progressive clouding of consciousness. This syndrome[9] is seen most frequently in association with chronic alcoholism, endemic pellagra, senility and cirrhosis of the liver. In our study of 150 cases the mortality was reduced from above 90 per cent to 15 per cent by nicotinic acid therapy. It should be emphasized, however, that these patients are usually left with organic memory defects. Most of these subjects are in the elder age group and their conditions are probably complicated by cerebral arteriosclerosis.

A relationship of thiamine, nicotinic acid and ascorbic acid to infantile paralysis,[10] delirium tremens[11] or Korsakoff's psychosis[12] has been suggested but, in my opinion, has not been proved. In all these, as in many other diseases, an associated or secondary vitamin deficiency may occur. In delirium tremens the decided increase in total metabolism raises the vitamin requirements to such an extent that an acute deficiency may be precipitated from which the patient may die unless attention is given to insuring adequate nutrition.

The value of alpha-tocopherol and pyridoxine in the syndromes of muscular dystrophy, amyotrophic lateral

3. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, J. A. M. A. **111:** 584 (Aug. 13) 1938. Spies, T. D.; Aring, C. D.; Gelperin, Jules, and Bean, W. B.: The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid, Am. J. M. Sc. **196:** 461 (Oct.) 1938. McLester, J. S.: Borderline States of Nutritive Failure, J. A. M. A. **112:** 2110 (May 27) 1939. Spies, T. D., and Aring, C. D.: Effect of Vitamin B_1 on the Peripheral Neuritis of Pellagra, ibid. **110:** 1081 (April 2) 1938. Sydenstricker.[9]

4. Jolliffe, Norman; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191:** 515 (April) 1936. Jolliffe, Norman, and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107:** 642 (Aug. 29) 1936. Goodhart, Robert, and Jolliffe, Norman: Effects of Vitamin B (B_1) Therapy on the Polyneuritis of Alcohol Addicts, ibid. **110:** 414 (Feb. 5) 1938. Jolliffe, Norman, and Goodhart, Robert: Beriberi in Alcohol Addicts, ibid. **111:** 380 (July 30) 1938. Jolliffe, Norman, and Rosenblum, L. A.: Circulatory Manifestations of Vitamin Deficiency: Diagnosis, Treatment and Prevention, M. Clin. North America **23:** 759 (May) 1939. Jolliffe, Norman: The Diagnosis, Treatment, and Prevention of Vitamin B_1 Deficiency, Bull. New York Acad. Med. **15:** 469 (July) 1939; Recent Advances in the Therapeutic Use of the B Vitamins, M. Clin. North America **24:** 733 (May) 1940. Fein, H. D.; Ralli, Elaine P., and Jolliffe, Norman: Peripheral Neuropathy Due to Vitamin B_1 Deficiency in Diabtes Mellitus, J. A. M. A. **115:** 1973 (Dec. 7) 1940. Wechsler, I. S.: Unrecognized Cases of Deficiency Polyneuritis (Avitaminosis?): Preliminary Report, M. J. & Rec. **131:** 441 (May 7) 1930; Etiology of Polyneuritis, Arch. Neurol. & Psychiat. **29:** 813 (April) 1933. Vorhaus, M. G.; Williams, R. R., and Waterman, R. E.: Studies on Crystalline Vitamin B_1: Experimental and Clinical Observations, J. A. M. A. **105:** 1580 (Nov. 16) 1935. Borson, H. J.: Clinical Application of the Thiochrome Reaction in the Study of Thiamin (B_1) Deficiency, Ann. Int. Med. **14:** 1 (July) 1940. Fantus, Bernard, editor, with Traut, E. F., and Greenbaum, R. S.: The Therapy of the Cook County Hospital: The Therapy of Subvitaminosis B_1, J. A. M. A. **115:** 450 (Aug. 10) 1940. Meiklejohn, A. P.: Is Thiamine the Antineuritic Vitamin? New England J. Med. **223:** 265 (Aug. 22) 1940. Brown, M. R.: Alcoholic Polyneuritis; An Evaluation of Treatment at the Boston City Hospital from 1920 Through 1938, J. A. M. A. **116:** 1615 (April 12) 1941. Spies and Aring.[3]

5. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Polioencephalitis Hemorrhagica Superior): Its Alcoholic and Nonalcoholic Incidence, J. Path. & Bact. **48:** 245 (March) 1939. Alexander, Leo: Topographic and Histologic Identity of the Experimental (Avitaminotic) Lesions of Wernicke with Lesions of Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Men, Arch. Neurol. & Psychiat. **42:** 1172 (Dec.) 1939. Jolliffe, Norman: Neuropsychiatric Manifestations of Vitamin Deficiencies, read at the Section of Medicine, New York Academy of Medicine, Jan. 21, 1941; to be published. Jolliffe, Wortis and Fein.[6]

6. Jolliffe, Norman; Wortis, Herman, and Fein, H. D.: The Wernicke Syndrome, J. Nerv. & Ment. Dis. **93:** 214 (Feb.) 1941; Arch. Neurol. & Psychiat., to be published.

7. Matthews, R. S.: Pellagra and Nicotinic Acid, J. A. M. A. **111:** 1148 (Sept. 24) 1938. Sydenstricker, V. P.; Schmidt, H. L.; Fulton, M. C.; New, J. S., and Geeslin, L. E.: Treatment of Pellagra with

[Footnote 7 continued in next column]

Nicotinic Acid: Observations in Forty-Five Cases, South. M. J. **31:** 1155 (Nov.) 1938. Spies, T. D.; Grant, J. M.; Stone, R. E., and McLester, J. B.: Recent Observations on Treatment of 600 Pellagrins, with Special Emphasis on Use of Nicotinic Acid in Prophylaxis, ibid. **31:** 1231 (Dec.) 1938. Spies, T. D.; Vilter, R. W., and Ashe, W. F.: Pellagra, Beriberi and Riboflavin Deficiency in Human Beings, J. A. M. A. **113:** 931 (Sept. 2) 1939. Jolliffe: Recent Advances;[2] Newer Knowledge.[2] Spies, Aring, Gelperin and Bean.[3]

8. Jolliffe, Norman; Bowman, K. M.; Rosenblum, L. A., and Fein, H. D.: Nicotinic Acid Deficiency Encephalopathy, J. A. M. A. **114:** 307 (Jan. 27) 1940.

9. Jolliffe, Norman: The Effects of Vitamin Deficiency on Mental and Emotional Processes, A. Research Nerv. & Ment. Dis., Proc. (1938) **19:** 144, 1939. Cleckley, H. M.; Sydenstricker, V. P., and Geeslin, L. E.: Nicotinic Acid in the Treatment of Atypical Psychotic States Associated with Malnutrition, J. A. M. A. **112:** 2107 (May 27) 1939. Sydenstricker, V. P.: The Present Status of Nicotinic Acid, Arch. Int. Med. **67:** 746 (April) 1941. Jolliffe, Bowman, Rosenblum and Fein.[8]

10. Heaslip, W. G.: Vitamin C Nutrition and Susceptibility to Diphtheria as Possible Factors in the Epidemiology of Poliomyelitis, Australian J. Exper. Biol. & M. Sc. **16:** 287 (Dec.) 1938. Jungeblut, C. W.: A Further Contribution to Vitamin C Therapy in Experimental Poliomyelitis, J. Exper. Med. **70:** 315 (Sept.) 1939.

11. Wortis, Herman: Delirium Tremens, Quart. J. Stud. on Alcohol **1:** 251 (Sept.) 1940. Rosenbaum, Milton; Piker, Philip, and Lederer, Henry: Delirium Tremens: Study of Various Methods of Treatment, Am. J. M. Sc. **200:** 677 (Nov.) 1940. Jolliffe, Norman, and Wortis, Herman: Encephalopathia Alcoholica: An Evaluation of Vitamin Therapy, read at the Annual Meeting of the American Psychiatric Association, Richmond, Va., May 9, 1941, to be published. Wortis, Herman, and Jolliffe, Norman: Present Status of Vitamins in Nervous Health and Disease, New York State J. Med., to be published. Wortis, Herman; Wortis, S. B., and Marsh, F. I.: Vitamin C Studies in Alcoholics, Am. J. Psychiat. **94:** 891 (Jan.) 1938; Role of Vitamin C in Metabolism of Nerve Tissue, Arch. Neurol. & Psychiat. **39:** 1055 (May) 1938. Alexander, Leo; Pijoan, Michel; Schube, P. J., and Moore, Merrill: Cevitamic Acid Content of Blood Plasma in Alcoholic Psychoses, ibid. **40:** 58 (July) 1938. Spies, Aring, Gelperin and Bean.[3]

12. Bowman, K. M.; Goodhart, Robert, and Jolliffe, Norman: Observations on the Role of Vitamin B_1 in the Etiology and Treatment of Korsakoff Psychosis, J. Nerv. & Ment. Dis. **90:** 569 (Nov.) 1939. Jolliffe, Wortis and Fein.[6]

sclerosis and paralysis agitans has recently been the subject of conflicting reports.[13] In all disorders which may be viewed as syndromes rather than as disease entities a positive response to treatment in but few patients may be significant, for it may indicate a curable disease entity within a syndrome previously considered irreversible. It seems reasonable, therefore, and in view of the conflicting reports and of the progressive nature of these syndromes, to give the vitamins on an experimental basis under carefully controlled conditions.

Syndromes collectively labeled paralysis agitans, while not directly fatal, usually follow a progressive course, the victims eventually becoming helpless. Since muscular rigidity and weakness are characteristic of paralysis agitans, and since pyridoxine is involved in muscle metabolism, it seemed worth while to test its effect in this syndrome. I therefore selected 15 patients having paralysis agitans, all of whom were chairfast or bedfast, 10 for more than three years, and administered to each 50 or 100 mg. of pyridoxine parenterally, either daily or every other day for at least four weeks. Of the 15 patients 4 showed definite objective improvement. These results were reported in April 1940 before the Minnesota State Medical Association.[14] Similar results were reported a short time later by Spies, Hightower and Hubbard.[15] Two of the 4 patients who showed objective improvement have since died, one following a fracture of the femur and the other following a myocardial infarction; the improvement in these 2 patients was maintained until the onset of the terminal illness. The improvement in the third patient has now been maintained for more than fourteen months, although he must receive pyridoxine parenterally three times a week for which saline, thiamine or nicotinamide cannot be substituted. The fourth patient has had a regression, so that now the tremors and rigidities are about the same as they were at the start of the treatment.

In reporting on these 15 helpless patients I noted that "thus far objective beneficial results . . . have been limited to the lessening of rigidities and increase in strength in patients whose complete disability was of less than three years' duration." Since then I have treated 46 ambulatory patients having paralysis agitans with pyridoxine, without selection as to age, type or degree of disability within ambulatory limits. Fourteen patients, all of whom showed no improvement, abandoned the treatment in less than three weeks. Shorter trials of therapy, such as recently reported by Zeligs,[16]

TABLE 1.—*Neuropsychiatric Disorders for Which There Is Substantial Evidence That Vitamin Deficiency May Play an Etiologic Role*

Disease or Syndrome	Predominant Vitamin Deficiency	Value in Therapy	References to Literature
A neurasthenic syndrome	(a) Thiamine	Yes	Williams, Mason and Smith.[2] Williams, Mason, Wilder and Smith.[2] Jolliffe, Goodhart, Gennis and Cline.[2] Jolliffe.[2]
	(b) Nicotinic acid	Yes	Spies, Bean and Stone.[3] Spies, Aring, Gelperin and Bean.[3] McLester.[3] Spies and Aring.[3] Sydenstricker.[9]
Polyneuropathy	Thiamine	Yes	Spies and Aring.[3] Jolliffe, Colbert and Joffe.[4] Jolliffe and Colbert.[4] Goodhart and Jolliffe.[4] Jolliffe and Goodhart.[4] Jolliffe and Rosenblum.[4] Jolliffe.[4] Fein, Ralli and Jolliffe.[4] Wechsler.[4] Vorhaus, Williams and Waterman.[4] Borson.[4] Fantus.[4] Meiklejohn.[4] Brown.[4]
Ophthalmoplegia of Wernicke's syndrome	Thiamine	Yes	Campbell and Biggart.[5] Alexander.[5] Jolliffe, Wortis and Fein.[6] Jolliffe.[5]
Pellagra psychosis	Nicotinic acid	Yes	Matthews.[7] Sydenstricker, Schmidt, Fulton, New and Geeslin.[7] Spies, Aring, Gelperin and Bean.[3] Spies, Grant, Stone and McLester.[7] Spies, Vilter and Ashe.[7] Jolliffe (Recent Advances; Newer Knowledge).[2]
Nicotinic acid deficiency, encephalopathy	Nicotinic acid	Yes	Jolliffe, Bowman, Rosenblum and Fein.[8] Jolliffe.[9] Cleckley, Sydenstricker and Geeslin.[9] Sydenstricker.[9]
Infantile paralysis	(a) Ascorbic acid	No	Heaslip.[10] Jungeblut.[10]
	(b) Thiamine	No	McCormick, W. J.: Poliomyelitis, Canad. M. A. J. **38**: 260 (March) 1938. Hamburger, F.: B1-Vitaminnahrung zur Verhutung der Poliomyelitis? Wien. klin. Wchnschr. **51**: 825 (Aug. 5) 1938. Jungeblut.[10]
Delirium tremens	(a) Thiamine	No	Wortis.[12] Rosenbaum, Piker and Lederer.[11] Jolliffe and Wortis.[11] Wortis and Jolliffe.[11] Spies, Aring, Gelperin and Bean.[3]
	(b) Nicotinic acid	No	Rosenbaum, Piker and Lederer.[11] Jolliffe and Wortis.[11] Wortis and Jolliffe.[11] Spies, Aring, Gelperin and Bean.[3]
	(c) Ascorbic acid	No	Wortis, Wortis and Marsh.[11] Alexander, Pijoan, Schube and Moore.[11]
Korsakoff psychosis	Thiamine	No	Bowman, Goodhart and Jolliffe.[12] Jolliffe, Wortis and Fein.[6]
Muscular dystrophy (some types)	(a) Alpha-tocopherol	Exp.*	Bicknell.[13] Stone.[13] Spies and Vilter.[13] Donovan.[13] Shelden, Butt and Woltman.[13] Ferrebee, Klingman and Frantz.[13]
	(b) Pyridoxine	Exp.	Ferrebee, Klingman and Frantz.[13] Antopol and Schotland.[13] Bakwin.[13]
Amytrophic lateral sclerosis (some types)	(a) Alpha-tocopherol	Exp.	Bicknell.[13] Spies and Vilter.[13] Ferrebee, Klingman and Frantz.[13] Wechsler.[13] Denker and Scheinman.[13]
	(b) Pyridoxine	Exp.	Shelden, Butt and Woltman.[13]
Paralysis agitans (some types)	Pyridoxine	Exp.	Jolliffe.[14] Spies, Hightower and Hubbard.[15] Zeligs.[16] Wortis.[17] Baker.[13]

* Exp. indicates experimental.

13. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**: 10 (Jan. 6) 1940. Stone, Simon: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on the Use of Vitamin E (Wheat Germ Oil), J. A. M. A. **114**: 2187 (June 1) 1940. Spies, T. D., and Vilter, R. W.: A Note on the Effect of Alpha-Tocopherol (Vitamin E) in Human Nutrition, South. M. J. **33**: 663 (June) 1940. Donovan, G. E.: Lordosis and Muscular Dystrophy, Lancet **2**: 162 (Aug. 10) 1940. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, Proc. Staff Meet., Mayo Clin. **15**: 577 (Sept. 11) 1940. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B6; Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, J. A. M. A. **116**: 1895 (April 26) 1941. Antopol, William, and Schotland, C. E.: The Use of Vitamin B6 in Pseudohypertrophic Muscular Dystrophy, ibid. **114**: 1058 (March 23) 1940. Bakwin, Harry: Personal communication to the author on negative response from pyridoxine therapy in muscular dystrophy. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**: 948 (March 16) 1940; The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**: 765 (Dec.) 1940. Denker, P. G., and Scheinman, Leonard: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), J. A. M. A. **116**: 1893 (April 26) 1941. Baker, A. B.: The Treatment of Paralysis Agitans with Vitamin B6 (Pyridoxine Hydrochloride), ibid. **116**: 2484 (May 31) 1941. Jolliffe.[14] Spies, Hightower and Hubbard.[15] Zeligs.[16] Wortis.[17]

14. Jolliffe, Norman: Clinical Aspects of Vitamin B Deficiencies, Minnesota Med. **23**: 542 (Aug.) 1940.

15. Spies, T. D.; Hightower, D. P., and Hubbard, L. H.: Some Recent Advances in Vitamin Therapy, J. A. M. A. **115**: 292 (July 27) 1940.

16. Zeligs, M. A.: Use of Pyridoxine Hydrochloride (Vitamin B6) in Parkinsonism, J. A. M. A. **116**: 2148 (May 10) 1941.

who gave "daily doses of 50 to 100 mg. (repeated one to three times)" intravenously, are entirely inadequate for judging this form of therapy. The group of 32 patients who continued the treatment longer than three weeks, of whom 23 were economic cripples, has

TABLE 2.—*Ambulatory Patients with Paralysis Agitans: Pyridoxine Treatment for Three Weeks or More*

Group	Number	Improvement				Continuing Therapy
		None	Subjective	Objective	Return to Work	
Arteriosclerotic	6	5	1	0	0	1
Postencephalitic	10	4	6	4	2	6
Idiopathic	16	10	6	2	1	7
Total	32	19	13	6	3	14

shown, I believe, worth while results (table 2). The most conservative estimate of improvement would be to take as a criterion the 10 per cent who showed economic rehabilitation (one as a farm hand, one as a clerk in a vegetable market, the third as an insurance broker). A less conservative estimate would be the 20 per cent who showed objective improvement. A far too liberal estimate would be the 40 per cent who show subjective improvement and are still willing to continue treatment that involves travel and parenteral administration. One of my associates [17] has studied 12 cases of long-standing parkinsonism (average duration ten and one-half years) and noted no beneficial results from adequate pyridoxine therapy.

The fact that the improvement in helpless patients previously reported on was limited to those with the idiopathic and arteriosclerotic types of the condition, while in the ambulatory series reported here improvement seems more frequent in the postencephalitic group, indicates that the entire series is still too small to allow definite conclusions to be drawn. It seems justifiable to say, however, that the syndrome of paralysis agitans, if not of too long duration, appears to include cases which are helped by pyridoxine.

Nutritional treatment of neuropsychiatric disorders consists of (1) general measures applicable to all and (2) specific therapy. The principles on which the general treatment is based are (*a*) that deficiency disease in man is usually not single but multiple and (*b*) that therefore adequate treatment does not consist of the administration of specific chemicals (crystalline vitamins), whether singly or in combination. All neuropsychiatric patients to whom specific therapy is to be given are therefore placed on the following regimen:

1. A full, nutritious diet of natural unrefined foods. To accomplish this, all vitamin-free or vitamin-poor foods are excluded from the diet. (These include sugar, candy, jellies, jams, white flour products, refined cereals, polished rice and alcoholic drinks). The patient is instructed to eat each day citrus fruit juices or tomato juice 360 cc., milk 720 cc., meat (including frequent servings of liver or pork muscle) 250 Gm., eggs 2, butter 45 Gm., salad (raw vegetables and fruit) 250 Gm., salad oil 15 cc. and potatoes 250 Gm. The balance of the diet is selected by the patient from cooked or raw vegetables, cooked or raw fruits, whole grain cereals and whole grain bread.

2. Vitamin supplements by mouth. Routinely the patients are given a fish liver oil in an amount containing 10,000 units of vitamin A and a source of the entire vitamin B complex. Such products as 30 Gm. of brewers' yeast, 20 Gm. of vegex, 45 cc. of aqueous liver extract or 60 Gm. of wheat germ cereal are preferred to synthetic products in capsule form from which some factors as yet impossible to encapsulate are likely to be missing.

3. Parenteral administration of the entire vitamin B complex. This practice is based on the empirical observation that these patients seem to do better when at least a quantity of the entire B complex is given parenterally. It is especially important when absorption or utilization of the vitamins may be impaired. I use as a routine 2 or 3 cc. of crude liver extract or liver residue as a vehicle for the specific vitamin prescribed and continue it as long as vitamins are administered parenterally. If injections are long continued local soreness may make it advisable to substitute for liver extract synthetic vitamins that can be given either intravenously or intramuscularly. For this purpose I use thiamine hydrochloride 10 mg., riboflavin 1 mg. and nicotinic acid amide 100 mg.

These disorders are complicated at times by gastrointestinal or other disturbances which prevent this routine from being followed. The diet may then be modified to meet the individual requirement, as much as possible of its nutritive qualities being retained. The vitamin A is increased to 20,000 units; in place of the bulky sources of the B complex crystalline vitamins are given twice daily in the following amounts: thiamine 2.5 mg., riboflavin 3.75 mg., nicotinic acid amide 25 mg., and 200 mg. of ascorbic acid is given in two doses.

TABLE 3.—*Specific Treatment of Neuropsychiatric Disorders with Vitamins*

Disease or Syndrome	Vitamin	Amount in Mg.	Route	Frequency	Comment
Neurasthenic	Thiamine	10 to 30	Parenteral	Daily	Trial of at least 3 weeks if less than 3 months' duration, if of longer duration trial of at least 3 months
	Nicotinic acid amide	100 to 300	Mouth	Daily	
Polyneuropathy					
Mild	Thiamine	10 to 30	Parenteral	Daily	10 days to 3 weeks
Moderate	Thiamine	20 to 50	Parenteral	2 times daily	3 to 6 weeks
Severe	Thiamine	20 to 100	Parenteral	2 times daily	3 to 6 weeks then in smaller doses until well after improvement ceases
Ophthalmoplegia of Wernicke's syndrome	Thiamine	50 to 100	Parenteral	3 times daily	2 to 7 days
Pellagra psychosis	Nicotinic acid	300 to 1,000	Mouth	Daily	1 to 4 weeks then continue smaller doses until complete recovery
Nicotinic acid deficiency, encephalopathy	Nicotinic acid	500 to 1,000	Mouth	Daily	3 to 7 days
	Nicotinic acid amide	100 to 200	Parenteral	Daily	3 to 7 days then continue smaller doses by mouth through convalescence
Muscular dystrophies	Pyridoxine	50 to 100	Parenteral	Daily	Trial of at least 3 months
Paralysis agitans	Pyridoxine	50 to 100	Parenteral	Daily	Trial of at least 1 month
Amyotrophic lateral sclerosis	Alpha-tocopherol	150 to 200	Mouth	Daily	Trial of at least 3 months
		100 to 150	Parenteral	Daily	

17. Wortis, Herman: Personal communication to the author.

Specific treatments recommended in table 3 are based on the principle that when biochemical or reversible anatomic lesions are present it is safer to err on the side of wasting the vitamin than to give too little for too short a period of time. If the patient has liver disease or diarrhea or is an alcoholic addict, the larger doses recommended in the table should be given. Clinical as well as experimental evidence indicates that in these conditions much larger doses of vitamins are required to produce maximal response than when absorption is unimpaired and the liver normal.

In view of recent expressions concerning toxic effects of vitamins, I believe it pertinent to state that in treating more than 3,000 patients with clinically manifest deficiency disease I have not observed any toxic effects when the vitamins were administered as a crystalline vitamin dissolved in saline solution without added preservatives, in the doses described, and while the patient was maintained with a good diet and the entire vitamin B complex (except, of course, the vasomotor phenomena of nicotinic acid). Drs. Borsook, McLester, Sebrell, Spies and Sydenstricker have informed me that their experiences have been similar. Dr. Borsook has administered by intravenous injection to each of 70 patients for at least three years 100 mg. of thiamine hydrochloride daily (except on Sundays and holidays) without observing any signs of toxicity. I have observed, however, local and general sensitivity to solutions of thiamine containing added preservatives. Cutaneous tests performed on these patients demonstrated sensitivity to the preservative and not to the thiamine. Subsequent administration of crystalline thiamine dissolved in saline solution was in no instance followed by either local or general sensitivity in the same patients. Two patients who were maintained with dextrose, saline solution and large doses of nicotinic acid and 4 patients who were maintained with a poor diet plus dextrose, saline solution, crystalline B vitamins in maintenance doses and large doses of nicotinic acid may possibly have manifested signs of nicotinic acid toxicity. I believe, however, that in these subjects deficiency of other vitamins is the more likely explanation.

CONCLUSION

No untoward effects have been observed after the therapeutic administration of any of the crystalline B vitamins to more than 3,000 patients.

39 East Seventy-Fifth Street.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. RUFFIN AND JOLLIFFE

DR. F. P. MOERSCH, Rochester, Minn.: We should be guided in our enthusiasm regarding vitamin therapy by the results obtained by careful leaders. As pointed out by Dr. Ruffin, overenthusiasm leads to confusion. The challenge that is being hurled at the indiscriminate users of vitamins in various neurologic disorders is unfortunate but may be justified. As the authors have stated, the so-called neurasthenic syndrome is probably one of the earliest and one of the most frequent manifestations of deficiency of both thiamine hydrochloride and nicotinic acid. Unfortunately, the clinical differentiation between the neurosis termed neurasthenia and the neurasthenic syndrome resulting from a vitamin deficiency is difficult. At the present time there is no simple laboratory method to aid us in this differentiation. To give the patient presenting a neurasthenic syndrome the benefit of doubt, vitamin therapy can be employed for a short period of time. If there is no prompt response to the treatment, it should be discontinued. If improvement does occur, the possibility of psychotherapy playing a role in the improvement must be weighed carefully. It may be advisable to avoid the term neurasthenic syndrome in connection with vitamin deficiency and employ some term such as vitamin asthenia to differentiate the condition from a purely functional disorder. Dr. Jolliffe deserves credit for being among the first to recognize the syndrome which he described as nicotinic acid deficiency encephalopathy. My own experience with this condition is rather limited. This is probably the result of our type of patients and partly of our failure to recognize the syndrome always. In this connection Dr. Snell and Dr. Butt, under the heading of "hepatic coma," have described a syndrome which has many of the features of nicotinic acid deficiency encephalopathy and which responds in dramatic manner to the administration of large quantities of dextrose with thiamine and nicotinic acid. Dr. Jolliffe is cautious in his statements regarding the value of vitamin therapy in the dystrophies and in amyotrophic lateral sclerosis. When such unrelated diseases as progressive muscular dystrophy, amyotrophic lateral sclerosis, multiple sclerosis and tabes dorsalis are placed in the same category and considered as examples of vitamin E deficiency, one has cause to stop and wonder. Our results in the treatment of these conditions by administration of various vitamins have been uniformly unsatisfactory. Our treatment of paralysis agitans with pyridoxine has also been discouraging.

DR. I. S. WECHSLER, New York: I am in some measure guilty of introducing vitamins in the treatment of neuropathies —not neuritis—and of other "degenerative" diseases of the nervous system. Absence of vitamins does not result in inflammation of nerve tissue either peripheral or central. No pathologist has ever demonstrated inflammatory changes in vitamin deficiencies. The word degeneration at best is a challenge, at worst meaningless. Many of the pathologic changes due to avitaminosis are reversible, the degree depending on the duration and extent of the privation. Negative results are not nearly so important as positive ones. There seems to be a certain specificity about vitamins, both as regards deficiencies and as regards therapeutic values. However, an apparent contradiction to this is that, while avitaminoses are specific, they are not usually isolated or unitary. Therefore, while the caution against "shotgun prescriptions" is correct, treatment with one vitamin alone is not always adequate. Vitamins, if effective, generally act rapidly. If results are not obtained within a reasonable period of time, there is no point in continuing treatment for months or years. As to so-called degenerative diseases of the central nervous system, such as multiple sclerosis or amyotrophic lateral sclerosis, I feel that they represent multiple syndromes of varying etiology. It is quite probable that only one of the syndromes is the result of vitamin deficiency, and therefore only isolated cases may be expected to respond to treatment. In view of the criticism leveled at clinical studies of avitaminoses, it may be well to recall that science does not consist alone in looking into test tubes. An accurate clinical observation honestly recorded is just as scientific as a laboratory experiment. Only a small proportion of a large number of cases of amyotrophic lateral sclerosis have responded to treatment with vitamin E. I do not now claim nor have I ever said that vitamin E cures the disease. Perhaps the worth of the studies will lie in the new approach to "degenerative" diseases. Our investigations have led to the perfection of a method for the determination of the tocopherol (vitamin E) level in the blood. The test may now be used in the study of normal persons, of patients ill with the disease, of the rate of absorption, of the relative therapeutic value of oral versus parenteral administration and of many other problems.

DR. C. A. MILLS, Cincinnati: I shall speak regarding two phases of vitamin therapy. One deals with sharp differences in optimal requirements at high and low temperatures and the other with thiamine overdosage and toxicity. In our laboratories at Cincinnati we have found that the thiamine requirement per gram of food for rats is twice as high at 91 F. as at 65 F. Preliminary studies have indicated a similar difference for pantothenic acid and pyridoxine. Last February and March I found that Panama residents were living under the same thiamine deficiency as my hot room laboratory animals. Using the thiochrome method for urinary thiamine excretion, I found most people on native foods to be excreting under 100 micrograms a day. It took six to eight days of thiamine feed-

ing (3 mg. a day) before this excretion rate rose above 1,000 micrograms a day, indicating a tissue saturation which I myself reached within one day at this dosage. Tropically grown meats seem to be deficient in thiamine, for test feedings with Panamanian pork loin gave much lower excretion rates than did those with pork imported from the United States. Tropical people seem doubly handicapped with respect to the B vitamins. Their requirements are higher and their supply more deficient than those of people living in cooler climates. These facts may help to explain the greater prevalence of B vitamin deficiency states in populations living under tropical or subtropical warmth. While in Panama my attention was called to repeated instances of thiamine toxicity. Many patients showed hyperthyroid-like symptoms—nervousness, insomnia, headache, tremor, rapid pulse, rise in blood pressure, emotional instability, nausea and sometimes vomiting. Since returning to Cincinnati I have come across even more severe thiamine reactions, with one death and several near-fatal collapses. These severe reactions all resulted from intramuscular thiamine injections in 10-50 mg. doses and seemed definitely allergic in character. In the one death, autopsy showed multiple ecchymoses beneath the pia over both cerebral hemispheres, with areas of encephalomalacia and perivascular hemorrhage. Dr. Leon Schiff witnessed one of these reactions and has consented to describe it briefly. Thiamine is very soluble and easily absorbable, with a normal daily requirement of about 2 mg. The medical profession might well bring the doses used down nearer this physiologic requirement, abandoning the 10 to 500 mg. dosages and the injection route of administration.

DR. MEYER ZELIGS, Cincinnati: Dr. Jolliffe has handled effectively the matter of general vitamin intake. His dietary regimen, comprising abundant foods rich in natural vitamins, plus the administration of known synthetic compounds—such as thiamine, riboflavin and nicotinic acid—constitutes an excellent method of assuring an adequate polyvitamin level in all patients under study. The addition to that regimen of specific synthetic fractions, such as pyridoxine or alpha-tocopherol, makes it easier to control such a study. When Dr. Jolliffe reported beneficial results with the use of vitamin B_6 in paralysis agitans, it was stated that within a few minutes there occurred much improvement, rigidity was decreased significantly and the patients were able to walk without the usual stiffness. It was on the basis of this report that I was moved to try the same form of therapy. Accordingly, a group of 15 patients with parkinsonism were selected, 10 of whom had the postencephalitic and 5 the arteriosclerotic type. Repeated daily doses of 100 mg. were administered intravenously to this group. This series of patients constituted an especially fitting one for such a study, since all of them had previously been under my observation for a period of six to eighteen months. Improvement could therefore be accurately evaluated by comparison with the previous condition of the entire group. Moreover, particular care was taken to avoid suggestive comment at the time of injection or thereafter, so that the psychologic effect of a "new" medicine would not be a factor in the therapeutic result. No change whatever was observed in the entire group. According to Dr. Jolliffe's communication, the duration of treatment has been lengthened to a period of at least four weeks, during which intravenous treatments with B_6 were given. This differs from his earlier reports, in which improvement was noted in a shorter time. I intend repeating this study and shall extend the duration of treatment over a longer period of time. I hope that I may be able to report something more encouraging at a later date.

DR. LEON SCHIFF, Cincinnati: I want to relate the experience to which Dr. Mills referred. This concerned a white school teacher, aged 45, with mild Raynaud's disease, hypertrophic arthritis and sciatica, who had during the course of eight months received fifty-seven injections of thiamine hydrochloride solution in doses of 25 mg. The injections were given intramuscularly. Three different commercial preparations were used in an attempt to avoid the nausea and vomiting which followed some of the injections. About a minute or two after her fifty-eighth injection she became nauseated, vomited, voided involuntarily and collapsed. Respiration ceased; she became pulseless, and I thought that she was dead. We immediately instituted artificial respiration, gave epinephrine hydrochloride intravenously and employed other measures used in shock, and the patient eventually recovered. She told us later that following the last three or four injections of the thiamine hydrochloride solution she had had some sneezing. Intradermal scratch tests done with two of the commercial preparations, including the one which induced the reaction, were strongly positive. It so happened that there was a different preservative in each of these two preparations. She was then tested with the preservatives, and the results were negative. She was tested with an aqueous solution of thiamine hydrochloride crystals on two different days and on both occasions gave a strongly positive test. The rapidity with which the systemic reaction occurred indicates that some of the thiamine hydrochloride solution may have entered a vein, although care had been exercised to give it intramuscularly. While this experience may be rare, it nevertheless makes us believe that skin testing patients who are about to receive thiamine hydrochloride solution intravenously may be a wise precautionary method.

DR. THOMAS T. MACKIE, New York: I have taken the liberty of requesting this opportunity of adding more emphasis to the thesis which Dr. Ruffin presented, and particularly with reference to the too strict interpretation of particular physical signs or symptoms as indicative of specific deficiencies. At a meeting some ten days ago of a group of us working in this field, it immediately became apparent in the discussion that those coming from different parts of the country associated different physical signs with different vitamin deficiencies. If one correlates with that what is certainly true in certain areas of this country, that there are fundamental variations in the type of diet which the people customarily ingest, the conflict is not as serious as it might appear to be superficially. Particularly is that true when one appreciates the present concept of the physiologic action of these specific food factors and their important relationship to the oxidation-reduction systems in intracellular metabolism. Furthermore there has developed not only this difference of opinion as to the specificity of physical signs but likewise a similar difference of opinion as to specificity of therapy. For example, the lesions in the nasal labial fold which are ascribed to ariboflavinosis respond in certain instances to the exhibition of nicotinic acid. The same situation applies to certain of the other factors as well. It is important, therefore, to realize that there may be a fundamental interrelation between these different substances of such a nature that the administration, let us say, of riboflavin to one individual will permit a sufficient restitution toward normal of intracellular metabolism to give an obvious therapeutic response, but that does not necessarily mean that the therapeutic response observed following the administration of a single crystalline substance is, strictly speaking, a true reaction to that particular material.

DR. NORMAN H. JOLLIFFE, New York: Dr. Moersch inquires regarding my experience with nicotinic acid deficiency encephalopathy in liver diseases. I have had the opportunity of seeing about half a dozen instances of this deficiency encephalopathy in patients having cirrhosis of the liver. This experience duplicates that of Snell and Butt as reported at the recent meeting of the Association of American Physicians. Dr. Zeligs pointed out his negative results with pyridoxine in paralysis agitans. I too can record a much larger series of negative results. As pointed out by Dr. Wechsler in the discussion and by me in my presentation, paralysis agitans is a syndrome consisting, in all probability, of several disease entities. A positive response in but few patients is more significant than negative responses in many patients. Dr. Zeligs gave daily doses of 50 to 100 mg. repeated one to three times. I do not believe an evaluation of therapy can be made, even provisionally, prior to three weeks of treatment. The treatment that I employed has been modified only in that this period of trial has been extended to four weeks. I wish to point out to Dr. Zeligs that the quotation, which he attributed to me, that "within a few minutes there was much improvement, rigidity was decreased significantly, and the patients were able to walk without their usual stiffness" appears nowhere in any of my published papers. Neither have I in a presentation before a society made this statement, even in the singular. Concerning the toxicity of the vitamins, it seems to me that the symptoms mentioned by Dr. Mills and

by Dr. Schiff are not those of toxicity but those of abnormal sensitivity. I believe any allergist would not hesitate so to label them and give epinephrine with full confidence in its efficacy. Proprietary preparations of vitamins when marketed in rubber capped vials suitable for several doses always contain a preservative. This preservative, for vitamins, is usually chlorobutanol. The two patients I have observed who showed these abnormal reactions to injections of vitamins were proved to be sensitive to the preservative and not to the vitamins. First, this was shown by skin tests, and second the administering of vitamins without added preservatives gave no symptoms.

THROMBOPHLEBITIS AND PULMONARY EMBOLISM

CLAUDE E. WELCH, M.D.
AND
HENRY H. FAXON, M.D.
Assistants in Surgery, Massachusetts General Hospital
BOSTON

Intravascular complications of surgical operations are common and, to a great extent, mysterious. Too often phlebitis is regarded simply as a nuisance and embolism as an act of providence. Yet the courses of these complications, and their relationships as well, are uniform enough in many cases to indicate the value of certain procedures designed either to prevent the disease or to treat it after it has developed.

Many problems present themselves immediately. Some of them are highly theoretical, others are entirely academic, but many are extremely practical. Unfortunately, even the most practical aspects must be based to a large extent on theory, because direct investigations of intravascular disorders and physiology are rare. This study has avoided as much theory as possible and has been elaborated about one central problem—the development of therapeutic guides.

To establish a comprehensive background, a survey was first made of 250 cases of thrombophlebitis of the lower extremities observed in the Massachusetts General Hospital during the five year period 1935-1939. A high proportion of these cases was seen by one or more members of the peripheral vascular clinic. From this group of cases a number of significant conclusions was drawn and unsolved problems specified. During the past two years we have attempted, as far as possible, to clarify these special points.

At the outset, we were concerned chiefly with these questions:

1. What laboratory measures or other clinical tests may be employed to diagnose phlebitis or to indicate when the disease has ceased?
2. What is the clinical course of a patient with uncomplicated thrombophlebitis treated by various methods?
3. In how many patients with phlebitis do pulmonary emboli develop and in which patients are they likely to occur?
4. Is there any therapeutic measure that will prevent the occurrence of emboli?

As far as possible, these questions will be answered.

PREVENTION

The prevention of phlebitis is, of course, a primary consideration but, as far as this study is concerned, only incidental. Here we are dealing chiefly with postoperative phlebitis. There is little new to add to this problem. Careful attention must be paid to correct any abnormalities such as cardiac failure, electrolyte imbalance and anemia. Varicose veins should be ligated preoperatively or controlled by compression bandages thereafter. Postoperatively, stasis of the blood stream must be avoided. This is promoted by frequent active movements of the legs in bed. It is not sufficient to have the patient get out of bed at an early postoperative date, for too frequently he will merely stand still, produce a static column of blood in the leg and increase the chances of thrombosis. Elevation of the foot of the bed during the early postoperative period will keep the veins of the calves relatively empty and prevent stasis in this important region.

Other measures to prevent thrombosis are of importance. The most recent has been the postoperative administration of heparin. Bancroft [1] has suggested the use of sodium thiosulfate intravenously, and also diets low in protein in an effort to diminish the clotting factors. We have used the thiosulfate occasionally, with no striking results as far as dissolution of a previously existing thrombosis is concerned. The protein in the blood stream is lowered with such difficulty and only after such protracted periods that it has hardly seemed wise to persist with this special diet. The postoperative use of thyroid to speed the pulse, and thereby prevent stasis, was tried extensively in this clinic for a year without any clear-cut conclusions and seems to us to possess no definite merit.

DIAGNOSIS

Ochsner [2] has distinguished between "thrombophlebitis," with its clear-cut signs of intravascular inflammation, and "phlebothrombosis," in which tenderness is slight and the temperature only slightly elevated. Theoretically, the diseases should behave differently. The ultimate results of the former should include more edema and more postphlebitic ulcers, while pulmonary emboli should be more common in cases of phlebothrombosis, in which the clot is not firmly anchored to the wall of the vein by inflammatory changes.

Practically, however, there are all gradations from the clearly purulent thrombophlebitis to pure thrombosis in which temperature, sedimentation rate and white count are all normal. Moreover, they all have in common the one most important dangerous characteristic—the tendency to extend proximally within the lumen of the involved vein.

While a few cases can clearly be defined as either phlebothrombosis or thrombophlebitis, the majority are equivocal. The term "thrombo-embolic disease" employed by many of the continental surgeons, emphasizes the essential similarity of these two types. We have found it impossible to attempt a definite separation but have called all cases of intravascular inflammation or thrombosis by the admittedly loose term "phlebitis." It is important to recognize, however, that the more closely the symptoms and signs aproach to those of true phlebothrombosis, the more dangerous is the situation.

It has been found to be much more important to locate the area of the vein involved in the pathologic process. For all practical purposes, this means that either the deep or the superficial veins should be specified as the site. Frequently deep phlebitis extends to involve portions or all the superficial systems, while the reverse is occasionally true. We have proved on

---

Owing to lack of space, this article has been abbreviated for publication in THE JOURNAL. The complete article appears in the authors' reprints.

Read before the Section on Surgery, General and Abdominal, at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 5, 1941.

1. Bancroft, F. W.; Stanley-Brown, Margaret, and Quick, A. J.: Postoperative Thrombosis and Embolism, Tr. South. S. A. **47**: 454, 1935.
2. Ochsner, Alton: Thrombophlebitis, Surgery **6**: 129, 1939.

the operating table that many cases in which the only obvious involvement is of the superficial veins present a thrombosis of the deep veins as well.

Clinical differentiation is therefore often difficult. Superficial phlebitis is easy to diagnose by the presence of tender subcutaneous thrombi along the course of the saphenous vein, but the detection of deep phlebitis may be hard. The importance of the diagnosis of deep phlebitis is exactly in reverse ratio to the ease with which it can be made. Meticulous examination as that followed by Culp [3] may show slight swelling of one leg or slight tenderness in the calf. Homans' [4] test of pain in the calf on forcible dorsiflexion of the ankle is occasionally positive when other signs are absent. Edema of the lower leg usually signifies thrombosis of the popliteal and lower portion of the femoral vein, while edema of the thigh indicates that the thrombosis extends at least as high as the external iliac vessels.

Laboratory studies are disappointing. The white count is extremely variable and undependable as far as diagnosis is concerned. We have formerly laid considerable stress on the sedimentation rate. It has also been capricious, varying from an extremely rapid to an unusually slow fall. About the only significance that can be attached to either the white count or the sedimentation rate is that a return to a normal level accompanies improvement in cases of true thrombophlebitis.

We have, in a series of cases, measured the circulation time of the blood in the legs by the method of Weiss and Robb,[5] in the hope that the time would be longer than normal if deep thrombosis was present. End points have not always been clear, and we have found the method unreliable.

It was therefore with great relief that we found the method of venography developed by Dos Santos [6] and elaborated by Bauer [7] and others [8] to be a valuable guide. We have come to place great reliance on the venogram. It must be made with an exact technic, and the reader must have some familiarity with the venographic picture in order to interpret it correctly. After some experience, it becomes simple to obtain and is an accurate guide. There are cases, however, in which the thrombosis is early and localized in the calf and in which clinical signs precede a positive venogram.

Quantitative measurements must be made in order to evaluate the severity of an attack of phlebitis and to determine when it has ceased. The amount of pain, of edema or of associated arterial spasm all offer means of comparison. Yet, for practical purposes, they are all difficult to estimate in a comparative fashion. Other ways are furnished by the number of days that a patient is kept in bed or in the hospital after the onset of the attack. Yet these figures will vary tremendously, depending on totally extraneous factors, such as the conservatism of the surgeon in charge or on the amount of crowding in the hospital beds. One criterion that we consider valuable is the duration of elevation of temperature. This is also a method of limited significance, since in occasional cases there is no accompanying elevation of temperature. A second criterion is the occurrence of pulmonary emboli during the acute phase, and a third, the persistence of chronic edema. As far as the first two considerations are concerned, the comparison is easy. The third is extremely hard to evaluate because these patients are difficult to trace accurately. It seems that until it is possible to present careful follow-up studies the behavior of the phlebitis during the acute stage must constitute the basis for any comparison of results.

What, then, may one learn concerning the length of disability and the occurrence of emboli as far as phlebitis is concerned? Superficial phlebitis will first be discussed briefly because the treatment of deep phlebitis has developed logically from the same considerations.

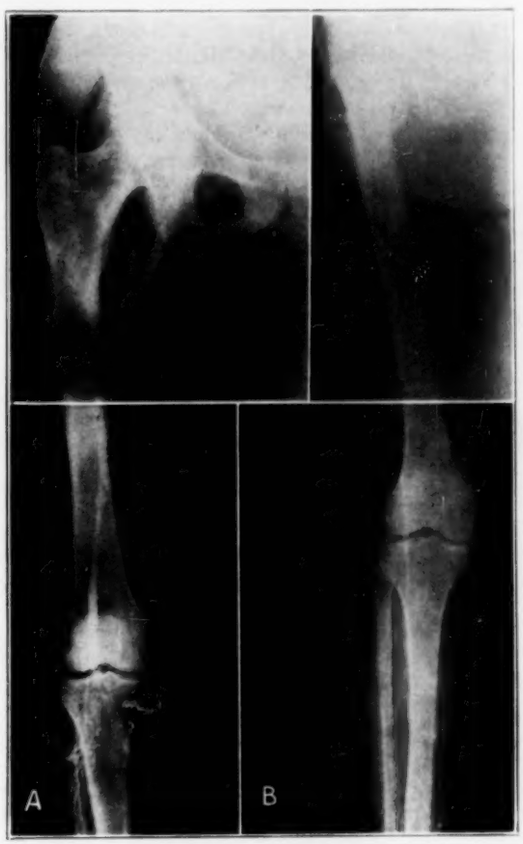


Fig. 1.—Differentiation of superficial and deep thrombophlebitis: *A*, normal venogram; *B*, venogram of a patient after operation who clinically had only superficial thrombophlebitis. Note lack of filling of the femoral vein in the venogram. Immediate ligation of the superficial femoral vein with removal of the thrombus. Recovery without embolic manifestations.

SUPERFICIAL PHLEBITIS

This may occur spontaneously, after direct trauma or after operation. If it originates from an infected ulcer or laceration, the phlebitis may be purulent. Usually, however, cultures of the clot will be negative. In any case, we believe that the best therapeutic procedure consists of ligation and division of the involved saphenous vein at its junction with the femoral or popliteal, as the case may be.

Ligation is urged for three reasons. 1. If the thrombosis is allowed to progress without treatment there is a tendency for the clot to progress proximally. The thrombus finally extends into the deep system of veins and may result in a thrombosis of the femoral vein. This may be prevented by section of the saphenous vein.

3. Culp, O. S.: Postoperative Venous Thrombosis and Pulmonary Embolism, Bull. Johns Hopkins Hosp. **67**: 1, 1940.
4. Homans, John: Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, New England J. Med. **224**: 179, 1941.
5. Robb, George, and Weiss, Soma: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, Am. Heart J. **8**: 650, 1933.
6. Dos Santos, J. C.: Direct Venography: Conception, Technique, First Results, J. internat. de chir. **3**: 625, 1938.
7. Bauer, Gunnar: A Venographic Study of Thrombo-Embolic Problems, Acta chir. Scandinav., 1940, supp. 61.
8. Dougherty, John, and Homans, John: Venography: A Clinical Study, Surg., Gynec. & Obst. **71**: 697, 1940.

2. There is also no doubt but that pulmonary emboli may originate from thrombi in the saphenous systems alone. These cases are not common. One patient included in this study had had three pulmonary infarcts until a partially thrombosed saphenous vein, in which a loose clot was found at operation, was tied. Barrow [9] has reported a fatal embolus arising from a saphenous vein, while Nobl [10] has stated that 0.5 per cent of all fatal emboli originate from the saphenous veins.

Finally, after ligation, it is possible and even desirable to make the patient immediately ambulatory, because the dangers of extension of thrombosis and further embolic manifestations are minimized. Unless there are other reasons for keeping him in the hospital, the patient is discharged the day after ligation has been performed.

DEEP PHLEBITIS

The problem of deep thrombophlebitis, however, is much more complicated than that of superficial phlebitis, and the therapeutics are correspondingly of more importance. Emboli are much more common and more serious. The well known sequelae of phlebitis—edema and ulcer—follow deep, rather than superficial, phlebitis.

Deep phlebitis may occur in the postoperative patient. It may follow direct or indirect trauma to the leg. It occurs spontaneously without any clear predisposing cause in many cases during the course of certain fevers or appears as an acute exacerbation in a leg previously the site of a phlebitic process.

Fig. 2.—Specimen of loose thrombus removed from the iliac vein by means of the Trendelenburg suction apparatus introduced through the superficial femoral vein. The patient had had a nearly fatal embolus before operation and none thereafter.

There may be some question as to whether all these types of phlebitis are similar enough to be grouped together. There does appear to be evidence that they are essentially alike. The duration of the disease, judged by the period of elevation of temperature, is essentially the same in the various types. The incidence of emboli is also remarkably constant in the different groups. Thus 17 out of 58 postoperative cases of deep phlebitis, 3 out of 10 traumatic cases and 14 out of 42 of the remaining cases presented emboli. The incidence of emboli to deep phlebitis in all these groups is very close to 1 in 3. Because of these similarities, all cases of deep phlebitis have been grouped together.

The most important feature to be discussed is the problem of pulmonary emboli. The length of stay in the hospital and the occurrence of late sequelae would be of little moment if emboli could be prevented. The importance of this aspect is shown by the high incidence of pulmonary emboli with deep phlebitis; 1 out of 3 patients has an embolus and 1 out of 25 will have a fatal embolus. The death rate is almost the same as that found by Miller and Rogers [11] in an earlier series of cases of phlebitis in this clinic, i. e. 7 deaths among 206 patients.

9. Barrow, D. W.: Fatal Pulmonary Embolus from Superficial Thrombophlebitis, Ann. Surg. **110:** 1118, 1939.
10. Nobl, G.: Prevention of Varicose Thrombophlebitis, Wien. klin. Wchnschr. **49:** 240, 1936.
11. Miller, R. H., and Rogers, Horatio: Postoperative Embolism and Phlebitis, J. A. M. A. **93:** 1452 (Nov. 9) 1929.

Pulmonary emboli vary tremendously in size and clinical symptoms. Massive pulmonary emboli, producing death immediately or within twenty-four hours, are relatively rare. We have been able to collect 128 proved cases from the Massachusetts General Hospital [12] in a thirteen year period. As far as therapeusis

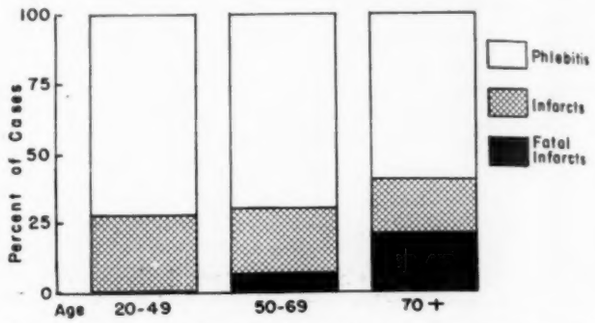


Fig. 3.—Incidence of deep thrombophlebitis of the legs and pulmonary infarcts with conservative therapy, according to age.

is concerned, the number of massive emboli associated with clinical phlebitis is unfortunately small (5.5 per cent in this series).

Clinical appreciation of thrombosis of the veins of the lower extremities has often been sluggish. Autopsy has often been of no value because the veins of the legs have not been examined. When this has been done, it is apparent that the large fatal emboli usually originate from the large veins of the lower extremities. Prettin [13] found that 133 out of 144 fatal emboli originated from the region drained by the inferior vena cava. Ninety-one of the patients had involvement of the femoral or iliac veins. Hampton and Castleman [14] have observed that "a very large percentage of emboli arise from symptomless thrombosis of the deep veins of the legs, usually in the popliteal region."

Formerly the uterine and the prostatic plexus were regarded as sources of fatal emboli. Castleman [15] believes that this view is incorrect. He states that, with the exception of pulmonary emboli originating from

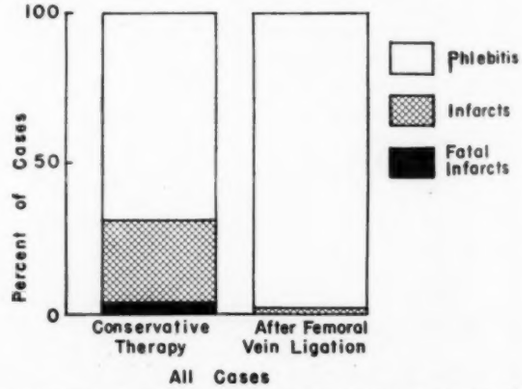


Fig. 4.—Incidence of embolism with thrombophlebitis of the legs after conservative therapy and after ligation of the femoral vein.

the heart, 95 per cent of all fatal emboli arise from the veins of the lower extremity, i. e. from the veins of the calf to the iliacs. This is attested by the fact that

12. Faxon, H. H., and Welch, C. E.: Massive Pulmonary Embolism, to be published.
13. Prettin, Fritz: Thrombosis and Fatal Pulmonary Emboli, Virchows Arch. f. path. Anat. **297:** 535, 1936.
14. Hampton, A. O., and Castleman, Benjamin: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings, Am. J. Radiol. **43:** 305, 1940.
15. Castleman, Benjamin: Personal communication to the authors.

he has found the source of the emboli to be in the legs in all but 2 cases in which he has done an autopsy.

Reduction in the incidence of pulmonary emboli will therefore require increasing attention to the veins of the lower extremities.

In contrast with the massive emboli, very small pulmonary emboli are extremely common, as Hampton and Castleman have proved. Many of them are subclinical in their symptomatology. Between these two classes of emboli are all others, not large enough to cause death yet enough to produce clinical symptoms and increased disability. The source of these emboli is not always clear but it seems likely, from autopsy studies of those patients who have succumbed to a massive embolus, that the minor emboli usually arise from the deep muscular veins of the calf.

There are several methods of treatment that may be employed. Each of them requires some discussion. The first, a time-honored method, consists of elevation of

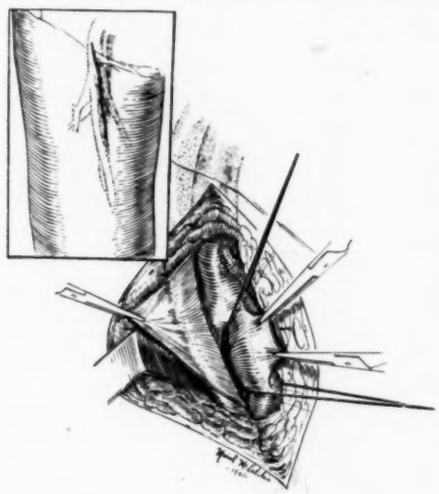


Fig. 5.—The superficial femoral vein is exposed, and control guy ligatures are passed above and below the site in which the vein is to be opened.

the leg on one or two pillows, the continuous application of hot wet packs to the entire leg, and administration of sedatives if pain is an important feature. Care must be taken that the packs do not become cold, for vasospasm is likely to be prominent in legs that are cold and damp. For this reason, a lighted cradle is often more satisfactory. Prolonged bed rest does not guarantee freedom from the danger of fatal embolus, although it is much safer than early mobilization.

Sympathetic block involves the repeated blocking of the sympathetic nerves by injection of procaine hydrochloride about the lumbar ganglions according to the method of Leriche,[16] and more recently popularized by Ochsner and deBakey.[17] The theory developed by the latter authors is that a localized area of thrombophlebitis initiates a state of vasospasm throughout the involved extremity. The flow of blood is therefore reduced, metabolites collect in the tissues and edema develops. The theory seems tenable; certainly in the worst cases of thrombophlebitis almost pulseless extremities develop. It is stated that vasospasm, unrelieved by heat, will respond rapidly to injection of procaine hydrochloride. It must be injected repeatedly until the phlebitis has subsided.

16. Leriche, René, and Kunlin, Jean: Immediate Treatment of Postoperative Phlebitis, Presse méd. **42**: 1481, 1934.
17. Ochsner, Alton, and deBakey, Michael: Thrombophlebitis: The Role of Vasospasm in the Production of Clinical Manifestations, J. A. M. A. **114**: 117 (Jan. 13) 1940.

Whether or not injection of procaine hydrochloride will diminish the number of pulmonary emboli associated with phlebitis is not clear. We have treated too few patients to be sure. Ochsner and deBakey report only 1 pulmonary infarct found in a series of 19 patients treated by this method. This may be partially explained by the fact that patients with active thrombophlebitis and fever are less apt to have emboli than those with phlebothrombosis, who have relatively little inflammatory reaction to anchor the clot to the venous wall.

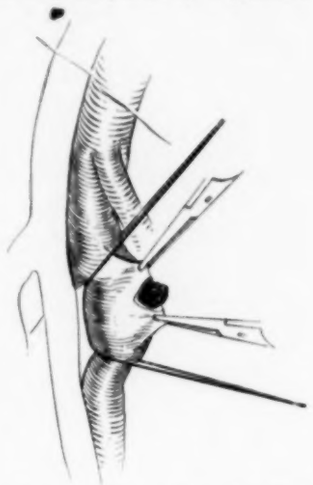


Fig. 6.—The vein is opened; fresh thrombus present.

Another method that has been developed is that of treatment with heparin. Murray[18] has been extremely optimistic as far as this method is concerned. Heparin will not dissolve previously existing white thrombi but will prevent the extension of any thrombosis and, according to Bauer,[7] will dissolve early red thrombi. Consequently, if heparin is instituted immediately after operation, patients should be expected to remain free of thrombosis. However, if phlebitis has already begun, there seems to be considerable doubt whether heparin could prevent the occasional dislodgment of an embolus.

Nor is there any reason why a thrombus should not develop on the basis of a preexisting phlebitis as soon as heparin therapy has been stopped.

One case is of considerable interest in this respect. A man aged 26 had a perfectly normal convalescence following an appendectomy until the eighth day, at which time he had a severe pulmonary embolus. Heparin therapy was immediately begun and was continued for ten days. No more embolic manifestations occurred, so heparin therapy was discontinued. Twenty-four hours later there was a well defined deep phlebitis involving the entire left leg. In another case, a pulmonary infarct was followed immediately by a fourteen day treatment with heparin. Shortly after the treatment ceased a fatal pulmonary embolus developed.

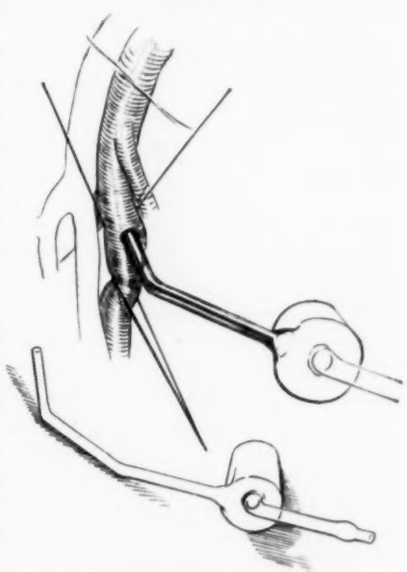


Fig. 7.—Other thrombi are removed by the Trendelenburg suction apparatus.

One other patient, given heparin after a pulmonary embolus had occurred, continued to have emboli as

18. Murray, G. O. W.: Heparin in Thrombosis and Embolism, Brit. J. Surg. **27**: 567, 1940.

soon as the administration of heparin was stopped. Emboli no longer occurred after ligation of the femoral vein.

These experiences with heparin lead us to our present opinion—that it is of value in the prevention of thrombosis and in the immediate treatment of an embolus, in order that there may be no extension of pulmonary thrombosis beyond the infarct. On the other hand, it cannot be depended on to prevent further emboli, once a thrombosis has been established.

Once treatment with heparin has been started, there is no way to be sure when it should be stopped. Usually we have arbitrarily continued it for ten days.

LIGATION OF THE DEEP VEIN

A fourth method of treatment involves the ligation of the femoral or iliac vein. This method of treatment was advocated by several German authors, including Kulenkampf [19] and Fründ,[20] who reported excellent results as far as the prevention of emboli was concerned. The method has also been advocated in this country by Homans,[21] Bancroft,[22] Taylor,[23] Sears [24] and others.

The operative procedure itself consists essentially in the actual opening of the femoral vein, the sucking out of any intravascular clot present and the ligation of the vein. Any or all of these details may be combined in the operation. The procedure is not simple and must be done with considerable care. If it were not for a few other considerations, this method would be the answer to the problem of emboli. These considerations are:

1. Will ligation of the femoral vein prevent pulmonary emboli?
2. Is it possible to tell which femoral vein should be ligated?
3. Are there any dangerous sequelae to ligation of the femoral vein?

The importance of the large veins of the calf as a source of emboli has already been stressed. It is our belief that increasing experience will show that the veins of the lower extremity are the source of a high percentage of emboli. The remaining emboli arise chiefly from the pelvis; branches of the internal iliac vein are involved. To place the ligature on the common iliac rather than on the femoral vein would reduce the number of emboli still further. Unquestionably, a few other emboli would occur, but they should be uncommon.

After a vein has been ligated, it has been shown that the thrombosis usually extends proximally until the next venous radicle is encountered. Thus, ligation of the common femoral vein will probably result in thrombosis extending to the bifurcation of the iliac veins. It is conceivable that this new thrombus could be the source of further emboli. Practically, we have never seen this happen and, on theoretical grounds, we doubt its occurrence. The theory is this: Thrombi are more apt to be dislodged if they are floating, one end free in the blood stream; if the flow of blood is completely stopped, protection from an embolus will be assured.

It seems best to divide the femoral vein rather than to ligate it in continuity. In several instances venograms taken a year after ligation of the femoral vein in continuity have shown no evidence of recanalization, and there is, then, no advantage in ligation without division.

It also seems important to stress the fact that the vein should be opened before it is ligated or clamped. Floating thrombi are difficult to detect by palpation through the wall of the vein, so that a tie or clamp might break off a freely floating thrombus.

Granted that the decision has been made to ligate the vein, the vein to be ligated must be chosen. Does an embolus necessarily arise from the leg that shows clinical phlebitis or is it more likely to arise from the leg that is not swollen? This is a difficult question to answer. In the few patients with concomitant emboli and unilateral phlebitis who have died of embolus and have come to autopsy, the evidence has pointed to the phlebitic process as the source of emboli. We have always first ligated the femoral vein of the leg that exhibits evidence of phlebitis. The presence or absence of a thrombosis on the other side may then be confirmed by a venogram. In two cases we have had to ligate both femoral veins.

The site of ligation of the vein is of importance. If possible, it is best to ligate above the thrombosis; if this is impossible, the proximal thrombus should be removed with the Trendelenburg suction device. We believe that the optimal site of exposure and ligation is the superficial femoral region. In this case there will be practically no postoperative edema. Ligation of the common femoral vein produces more edema. Homans advocates ligation of the iliac vein, believing postoperative edema to be rare. This involves a formidable dissection for a patient ill after an operation, so that we have not used it.

There certainly are dangers involved in the ligation of femoral veins. It is for this reason that the process cannot be carried out promiscuously. On the other hand, the great fear of a swollen leg is often overemphasized. From our experience, it appears that increased edema does not occur after ligation, or is very slight, as long as the patient is kept in bed. After mobilization edema will appear in approximately half the patients and must be controlled by compression bandages. In from three to six months the edema will practically disappear in nearly all cases. We have seen increasing pigmentation, superficial varices and a postphlebitic ulcer appear two years after division of a femoral vein. This is the only ulcer that has occurred in our series, though no patients have yet been followed more than two years. It seems likely that the incidence of postphlebitic ulcer would be as high in patients who had had no treatment for deep phlebitis, although no definite comparison is justifiable until this group of patients has been observed several years.

Ligation of the femoral vein should also shorten the period of disability from deep phlebitis, just as ligation of the saphenous vein has made it possible for patients with superficial phlebitis to become ambulatory more rapidly. This is perhaps a qualifiable indication for the procedure.

OTHER METHODS

Other methods of treatment have been proposed. The use of leeches, plaster of paris or compression bandages, roentgen rays and injection of typhoid bacilli all have had their advocates. We have not used any of them extensively. Papaverine has often been

19. Kulenkampf, D.: The Prevention of Severe and Fatal Emboli by Means of Emptying the Iliac Vein, Arch. f. klin. Chir. **193**: 727, 1939.
20. Fründ, H.: Thrombectomy as a Prophylaxis Against Pulmonary Emboli, Zentralbl. f. Chir. **64**: 1202, 1937.
21. Homans, John: Venous Thrombosis in the Lower Limbs: Its Relation to Pulmonary Embolism, Am. J. Surg. **38**: 316, 1937.
22. Bancroft, F. W.; Stanley-Brown, Margaret, and Chargaff, Erwin: Postoperative Thrombosis and Embolism, Ann. Surg. **106**: 868, 1937.
23. Taylor, K. P. A.: Pulmonary Emboli Following Injection of Varicose Veins, Am. J. Surg. **45**: 145, 1939.
24. Sears, J. B.: Experience with Femoral Vein Ligation for Prophylaxis of Postoperative Pulmonary Embolism, New England J. Med. **224**: 108, 1941.

employed in the treatment of emboli and appears to be of definite value. It seems to us to be a definite adjuvant type of therapy but not one that should be considered as a sole therapeutic measure.

CLINICAL APPLICATION

With these various methods in mind, it is now necessary to consider their clinical application in an attempt to determine the type of treatment indicated in the individual case. In this matter, we are concerned chiefly with the incidence of emboli and the prevention of death from this cause rather than with the less important criterion of the duration of the disease.

Given a patient with deep phlebitis, how apt is he to have an embolus? Generally speaking, the chances in this series are almost 1 in 3. The incidence is variable, however, depending on age. Of 53 patients under 50 years of age with deep phlebitis, 15 had an infarct (28 per cent). Of 56 patients in the age group 50 to 70, 16 had infarcts (31 per cent). Of 10 patients 70 years of age or over, 4 had infarcts (40 per cent). There appears to be a slight increase in the number of infarcts with advancing age.

The fatal emboli are more striking. There were no deaths under the age of 50 (with concomitant clinical deep phlebitis and emboli), but 3 deaths in the group from 50 to 70 years, and 2 in the oldest group. Since the period embodied in this study we have had 1 death of a patient aged 39 from an embolus originating from phlebitis. The death rate from deep phlebitis must be regarded as extremely low under the age of 50, about 7 per cent from 50 to 70 years and 20 per cent over that age.

A consideration of the type of operation preceding the phlebitis, or of the type of initiating trauma, has not been of comparable value as far as the prognostication of fatal emboli has been concerned. The fact that operations on the genitourinary tract are frequently followed by phlebitis and pulmonary emboli seems ascribable to the age of the patient rather than to the type of operation.

Phlebitis itself, then, constitutes a warning sign. A single infarct may then occur. The mortality of this infarct was 10 per cent in this series (2 deaths among 20 patients). Of the 18 patients surviving the first infarct, 11 had no more infarcts and 7 did have others; and 2 deaths resulted from the second infarct. This indicates that there will be as many deaths after the second infarct as after the first. Among 4 patients who have had 3 or more infarcts there have been no deaths, but all of them, with 1 exception, have had ligation of the femoral vein.

On the basis of this control series, the results following ligation of the femoral vein may be summarized briefly:

Ligations of the femoral vein in our clinic have been performed in 33 instances. The indications were pulmonary infarction associated with thrombophlebitis in 18 patients and thrombophlebitis in 15 patients over 40 years of age. There was a total of 36 infarctions observed before ligation; after the procedure there was 1 case in which a pleuritic pain lasting twenty-four hours suggested an infarct, although no shadow suggestive of an infarct could be discovered by roentgen examination.

From our previous experience we should have expected 5 infarcts and 1 death in the group of patients in whom ligation had been done for phlebitis if conservative therapy had been followed and at least 2 deaths in the group in whom ligation had been done for pulmonary infarction if operation had not been done.

We have thus become convinced of the wisdom of ligation of the deep venous channels, not only after pulmonary infarction associated with phlebitis but also as a method of prophylaxis against emboli. We also believe that it is essential, if the vein is to be ligated to do it as soon as the diagnosis of thrombophlebitis has been made; otherwise the entire femoral vein may become rapidly involved, as Bauer has shown. Moreover, the danger of pulmonary infarction is greatest soon after the onset of phlebitis, as shown by the careful analytical studies of Barker and his associates.[25] Every attempt should be made to interrupt the pathologic process before it involves the upper reaches of the femoral vein.

THERAPEUTIC GUIDE

From this mass of data we must next attempt to deduce suggestions for therapy:

1. *Superficial Phlebitis.*—Great care should be taken to exclude the presence of deep phlebitis. This means that a venogram should be made before operation. If the superficial veins only are involved and the patient is not in poor condition, ligation and division of the involved saphenous vein at its junction with the femoral or popliteal vein should be performed. Heat, elevation, compression bandages, incision and drainage of fluctuant areas and excision of thrombosed venous segments are adjuvant measures.

2. *Deep Phlebitis Not Associated with an Infarct.*—Elevation, heat and sedatives should be used in all cases. Lumbar block with procaine hydrochloride is certainly of value if vasospasm is considerable or pain is severe, and perhaps in all cases. In the group under the age of 40 no other treatment need be considered unless infarcts occur, for the chances of an initial infarct being a fatal one are extremely remote. On the other hand, from the ages of 50 to 70, early ligation of the femoral vein is indicated in view of the expected mortality of 7 per cent. Over the age of 70, there is an absolute indication for venous ligation because the expected mortality from embolus is 20 per cent.

3. *Deep Phlebitis Followed by an Infarct.*—The femoral vein should be opened, thrombi removed and the vein ligated. This is necessary to prevent the 10 per cent mortality of the second infarct.

4. *Pulmonary Infarct Without Evidence of Phlebitis.*—Venograms should be done on both sides. If a thrombosis can be detected, ligation of the corresponding femoral vein is indicated. A small infarct with minimal pulmonary symptoms may be treated conservatively. If the infarct is severe, heparin therapy should be instituted.

CONCLUSION

It is only fair to state that the operation of ligation of the femoral vein has appealed to us more strongly as we have become more familiar with the procedure. At present, we believe that the immediate decision to be made in any given case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein. If conservative therapy is employed, lumbar injection of procaine hydrochloride should be done if vasospasm is considerable. If the deep venous channels are interrupted, heparin is often of value

25. Barker, N. W.; Nygaard, K. K.; Walters, Waltman, and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **15**: 769 (Dec. 4) 1940.

administered postoperatively. It must be emphasized that these concepts may be modified greatly as our experience increases. The important fact is that thrombophlebitis is no longer observed passively but is now accepted as a disease that must be vigorously treated.

ABSTRACT OF DISCUSSION

DR. ALTON OCHSNER, New Orleans: The authors have emphasized that it is of importance to distinguish between phlebothrombosis and thrombophlebitis. In phlebothrombosis the patient does not appear very ill, but the condition is potentially dangerous because of the likelihood of embolism. The patient with thrombophlebitis is an individual who appears ill, whose extremity is quite swollen and who has a great deal of pain. The best treatment of thrombophlebitis is the overcoming of the vasospasm by procaine block of the regional sympathetic ganglions. My associates and I have treated 71 patients who had thrombophlebitis. The most dramatic result was the relief of pain. Ninety per cent were permanently relieved of pain by the first procaine sympathetic block. The subsidence of fever was also dramatic. Approximately 65 per cent were fever free in forty-eight hours or less, 24 per cent in from three to five days, 7 per cent in from six to eight days, and 4 per cent had fever more than eight days. The relief of edema was also dramatic. Fifty-six per cent had normal extremities in four days or less, 32 per cent in from five to eight days, 8 per cent in from nine to ten days, and only 2 patients had edema as long as twelve days. All of these were patients with typical phlegmasia alba dolens who otherwise would have had fever and edema for a period of six to eight weeks and a possible persistent edema for the rest of their lives. Occasionally more radical measures, such as ligation, are necessary in thrombophlebitis. When suppuration occurs, tying of the vein proximal to the thrombophlebitic segment is required to prevent the dissemination of infected emboli. In phlebothrombosis the clotting is likely to occur in certain veins in which stasis is greatest. As the authors have emphasized, the presence of Homans' "dorsiflexion sign" suggests phlebothrombosis of the calf veins, because often phlebothrombosis originates in the plantar veins of the foot; demonstration of tenderness on the plantar aspect of the foot is of importance. It is a rule in our service that every patient who isn't doing well, who has an elevation of pulse out of proportion to the temperature or who has a sense of impending disaster, a point which I would emphasize, not only shall be given Homans' test but have all the plantar veins investigated. It is of importance postoperatively to prevent this condition, to prevent the stagnation of the veins of the lower extremity by not having these patients lie perfectly flat. Either the foot of the bed should be elevated or, if they are lying flat, the thighs should be flexed on the trunk and the leg elevated to prevent angulation of the veins at the pelvis and at the knee.

DR. CONRAD R. LAM, Detroit: I should like to add a word about one method of treatment which the authors have mentioned; namely, heparinization. I shall be particularly concerned with the management of the embolic manifestations of phlebitis. Since April 1939 Dr. McClure and I have treated 34 such patients, all of whom had good evidence of embolism, such as hemoptysis, pain in the chest, physical findings and x-ray signs. Thirty-two of these patients survived. One apparently died of the original large infarct, while the other had a second and fatal embolism after one week of heparin therapy. Last year we reported that the cost of heparin treatment was about the same as special nurses; namely, about $15 a day. Now, with additional commercial preparations on the market, the cost has come down considerably and it can be stated that the price of a day's supply of heparin may be only $6 or $7, or about the cost of a hospital room. It is probable that this material is of value in selected cases.

DR. HENRY H. FAXON, Boston: From what has been said, some of you might get the impression that only in patients with a clinical deep phlebitis need we fear the accident of massive embolism. I should like to correct any such idea. Dr. Welch and I found in reviewing the 128 cases of fatal pulmonary embolism that have occurred at our hospital during the last thirteen years that in only 5.5 per cent did the surgeon in charge realize that the condition was a deep phlebitis. It other words, almost 95 per cent of these patients had such bland phlebothromboses that it was not appreciated that they were potential candidates for fatal emboli. It is true that all of these patients must have had deep peripheral thromboses present, for otherwise they could not have suffered fatal pulmonary emboli. If we are to lower the deaths from massive embolism and discover the cases in which various corrective measures such as ligation of the femoral vein or other corrective steps can be taken, we must first do something in the way of study that will lead us to detect those patients who have bland thromboses. Furthermore, we should adopt some method of study that will provide us with the fullest information as to the status and extent of these thromboses. I would like to add a word of enthusiasm for the use of venograms to accomplish these two aims. It would seem from what is still a somewhat limited experience that the use of this diagnostic aid has probably contributed more to an understanding of the underlying pathologic condition in this field than any other step that has been put forward for many years.

THE SURGICAL TREATMENT OF HYPERTENSION: II

COMPARISON OF MORTALITY FOLLOWING OPERATION WITH THAT OF THE WAGENER-KEITH MEDICALLY TREATED CONTROL SERIES: A STUDY OF SEVENTY-SIX CASES FROM FIVE TO SEVEN YEARS AFTER OPERATION

WARD WILSON WOODS, M.D.
AND
MAX MINOR PEET, M.D.
ANN ARBOR, MICH.

In a previous paper [1] we presented the results of 350 consecutive cases of hypertension in which treatment was by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy.

Our purpose in the present paper is to compare the results of this operation with those of an analogous series in which treatment was by medical means alone.

The first 76 consecutive cases of our main series were chosen for this study because the postoperative period of from five to seven years seemed adequate to evaluate the results fully and because this time period lends itself to comparative study.

A careful review of the literature concerning the results of therapy and the mortality rate in hypertension reveals an unexpected degree of confusion. This confusion results chiefly from inadequate classification of the cases before and after therapy and an inadequate period of observation after the therapy.

The fundamental question in the mind of the physician confronted with a patient with hypertension is "What is the prognosis of a patient of a certain age, of a certain sex, with a certain level of hypertension and with or without certain organic changes?" No control series giving a complete answer to this question could be found. It has been necessary, therefore, to choose from the various reports a series which, from one definite and objective aspect, i. e. retinal changes, presents a classification of hypertensive patients into clearly defined groups, and which states, after an adequate period of post-therapeutic observation, the mortality of these patients. Wagener and Keith [2] have

From the Department of Surgery, Section of Neurosurgery, University of Michigan Medical School.

This study was aided by a grant from the Aaron Mendelson Trust Fund to the Section of Neurosurgery.

1. Peet, M. M.; Woods, W. W., and Braden, Spencer: The Surgical Treatment of Hypertension, J. A. M. A. **115**: 1875-1885 (Nov. 30) 1940.

2. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**: 317-430, 1939.

presented a five to nine year follow-up study of 219 cases of essential hypertension classified according to retinal changes. They state: "The present series of cases offers a good control for any specific form of therapy, as treatment consisted of general measures, especially with regard to diet and rest, and the regular use of certain sedatives."

In the tables are presented the comparative mortality statistics of Wagener and Keith on 219 patients treated medically and followed for from five to nine years and of our series of 76 consecutive patients operated on by one of us (M. M. P.) and followed for from five to seven years. The discrepancy between the length of the two studies (five to nine years as against five to seven years) does not obviate relatively accurate comparison for two reasons: First, the time span of the medically treated control group is calculated from the time of the first observation of the patient, whereas in our series it is calculated from the time of operation. By far the majority of our patients had been observed over a considerable period of time and had been given a trial of medical treatment before operation was even considered. Second, as is shown in the accompanying charts, the deaths occurring after seven years in the control series were so few that their inclusion in the statistics does not alter the totals significantly.

A factor which cannot be controlled in the comparison of these two series is the selection of patients. Presumably the patients of Wagener and Keith were unselected and consecutive. Our patients were, by necessity, selected in that they were in sufficiently good physical condition to permit operation. Briefly, the criteria for selection for operation were:

Age: under 60 years, preferably under 50.

Renal function: nonprotein nitrogen of the blood under 45 mg. per hundred cubic centimeters, urine concentration above 1.012 and urea clearance above 40 per cent of normal.

Cardiac status: a compensated heart.

All patients had "essential" or "malignant" hypertension, i. e. a primary type of high blood pressure for which no organic cause could be found. Among the early patients with hypertension several exceptions to these criteria were made, since at that time our concept of an operable patient was still in a formative period. A very high blood pressure has never been a contraindication to operation, as will be shown in the second portion of this paper. Unfortunately, the Wagener-Keith control series of medically treated patients is not presented completely in regard to the cardiac status, renal status and blood pressure levels of the patients. A reservation regarding selection must then be held in mind in a comparison of the results tabulated.

MORTALITY STATISTICS

The classification of hypertensive patients according to observable retinal changes is an excellent one. It offers a means whereby the diffuse arteriolar disease of hypertension can be directly and easily observed and thus the degree of severity of the process can be evaluated.

It still remains to be seen whether or not the present interpretation and classification of fundus changes offer a true means of prognosis in hypertension.

Keith[3] originally divided patients with hypertensive disease into four groups. We have followed this grouping because of its common usage rather than its complete acceptability as a means of differential diagnosis and prognosis. Briefly, group 1 consists of those patients with diffuse arteriolar disease and mild hypertension who have no definite symptoms, no cardiac or renal failure and whose retinal arterioles exhibit a mild grade of narrowing and chronic sclerosis. Group 2 consists of those patients with a relatively higher blood pressure, with symptoms such as headache and increased nervousness, whose retinal arterioles show a more significant grade of narrowing and sclerosis but without angiospasm. Group 3 consists of those patients with a relatively high blood pressure, with definite symptoms and whose retinal arterioles show unmistakable angiospastic narrowing. In this group are included also those with angiospastic retinitis without measurable papilledema. Group 4 includes those with measurable papilledema and the concomitant diffuse angiospastic retinitis with varying degrees of chronic sclerosis of the arterioles.

TABLE 1.—*Number and Sex of Patients*

Keith Hypertension Group	Male		Female		Total	
	Wagener-Keith	Peet	Wagener-Keith	Peet	Wagener-Keith	Peet
1	7	0	3	4	10 (4%)	4 (5%)
2	14	6	12	9	26 (12%)	15 (20%)
3	22	11	15	22	37 (17%)	33 (43%)
4	99	11	47	13	146 (67%)	24 (32%)
Totals	142	28	77	48	219	76

TABLE 2.—*Age* *

Keith Hypertension Group	Range in Years		Mean Years	
	Wagener-Keith	Peet	Wagener-Keith	Peet
1	30-65	38-48	55	43
2	21-59	18-57	41	39
3	22-57	23-55	42	42
4	8-64	21-57	40	41

* Wagener-Keith: age at time of first examination; Peet: age at time of operation.

It is suggested that, in order to simplify and make purely objective the classification of essential hypertension according to ocular changes in the fundus the following four groups be adopted (substituting a group with normal fundi, consolidating those with purely arteriolar sclerotic changes into another group and basing the last two groups on the presence of angiospasm or papilledema): group 1, normal fundus; group 2, arteriolar sclerosis without angiospasm; group 3, unmistakable angiospasm with or without arteriolar sclerosis, hemorrhages or exudates, and group 4, papilledema. It will be shown later that the prognostic value of this classification from the surgical point of view is greater than that of the original classification of Keith and has the added advantage of being purely objective rather than of including such variables as level of blood pressure and subjective symptoms. For the purpose of comparison, however, the funduscopic groupings referred to in the body of this paper will be those of Keith's original classification.

In a comparison of the relative numerical distribution of the two series according to the Keith hypertension grouping (table 1), it may be seen that the percentages in groups 1 and 2 are approximately equal. Wagener and Keith have a larger percentage in group 4,

3. Keith, N. M.: Cardiovascular Diseases in Relation to the Retina, Tr. Am. Acad. Ophth. **37**: 37-49, 1932.

whereas in our series the larger percentage is in group 3. It should be noted, however, that both series have the greatest number of cases in the two groups showing the most "serious" retinal changes (Wagener-Keith 84 per cent and Peet 75 per cent in groups 3 and 4).

TABLE 3.—*Living Patients*

A. Patients Alive *

Keith Hypertension Group	Total Patients Studied		Total Patients Alive	
	Wagener-Keith	Peet	Wagener-Keith	Peet
1	10	4	6 (60%)	4 (100%)
2	26	15	9 (34%)	6 (40%)
3	37	33	3 (8%)	21 (64%)
4	146	24	1 (1%)	8 (33%)
Totals	219	76	19 (9%)	39 (51%)

B. Sex of Living Patients

Keith Hypertension Group	Male		Female	
	Wagener-Keith	Peet	Wagener-Keith	Peet
1	4 (57%)	0 (0%)	2 (66%)	4 (100%)
2	4 (28%)	1 (17%)	5 (42%)	5 (55%)
3	2 (9%)	7 (64%)	1 (6%)	14 (64%)
4	0 (0%)	3 (27%)	1 (2%)	5 (38%)
Totals	10 (7%)	11 (39%)	9 (12%)	28 (58%)

* Keith-Wagener: alive five to nine years after first examination; Peet: alive five to seven years after time of operation.

Sex distribution (table 1) reveals 65 per cent males in the Wagener-Keith series as against 36 per cent in our series. Since it is well known that males tolerate hypertension less well than females, this disproportion of males and females in the two series would seem

TABLE 4.—*Deaths*

A. Patients Dead *

Keith Hypertension Group	Total Patients Studied		Total Patients Dead	
	Wagener-Keith	Peet	Wagener-Keith	Peet
1	10	4	4 (40%)	0 (0%)
2	26	15	17 (65%)	9 (60%)
3	37	33	34 (92%)	12 (36%)
4	146	24	145 (99%)	16 (67%)
Totals	219	76	200 (91%)	37 (49%)

B. Sex of Patients Dead

Keith Hypertension Group	Male		Female	
	Wagener-Keith	Peet	Wagener-Keith	Peet
1	3 (43%)	0 (0%)	1 (33%)	0 (0%)
2	10 (71%)	5 (83%)	7 (58%)	4 (44%)
3	20 (91%)	4 (36%)	14 (93%)	8 (36%)
4	99 (100%)	8 (73%)	46 (98%)	8 (62%)
Totals	132 (93%)	17 (61%)	68 (88%)	20 (42%)

* Wagener-Keith: died five to nine years after first examination; Peet: died five to seven years after time of operation.

to be of considerable importance in the ultimate mortality. Careful analysis, however, of table 4 B demonstrates a relatively small difference in mortality between the two sexes in the control group (93 per cent males as against 88 per cent females).

There is a remarkably close correspondence of the mean ages per group in the two series (table 2). It is interesting to note that in group 1 the age is more advanced than in the other three groups, the mean ages being practically identical both in the control and in the surgical series.

Tables 3, 4 and 5 demonstrate the definitely lower mortality among hypertensive patients treated surgically. Thus, analysis of the mortality rates after five years (table 5) shows that the total mortality for the control group is 87 per cent as against 47 per cent for the surgically treated group. These percentages, however, are not strictly comparable because of two factors: surgical selection and the larger percentage in group 4 in the medically treated group. Therefore, analyzing the mortality rates more exactly by hypertension groups, one finds that in group 4 99 per cent of the control series were dead, contrasted with 66.5 per cent in the surgically treated series. In group 3 80 per cent of those treated medically died within five years, whereas only 36 per cent of the surgically treated patients died. In group 1 the mortality for the medical control series was 30 per cent, contrasted with no deaths in the surgical group—which, however, included only 4 cases. It is in group 2 (those patients with high blood pressure and retinal arteriolar sclerosis) that the mortality of the surgical treated patients (60 per cent) exceeds that of the medically treated group (46 per cent). This difference becomes

TABLE 5.—*Deaths Within a Given Number of Years*

Years	Group 1		Group 2		Group 3		Group 4	
	Wagener-Keith	Peet	Wagener-Keith	Peet	Wagener-Keith	Peet	Wagener-Keith	Peet
1	10%	0	12%	33% (1 operative)	35%	6% (1 operative)	79%	37.5% (2 operative)
2	20%	0	23%	46%	67%	12%	88%	50%
3	30%	0	38%	46%	78%	21%	94%	62.5%
4	30%	0	42%	53%	78%	24%	98%	66.5%
5	30%	0	46%	60%	80%	33%	99%	66.5%

less striking, however, on examination of the survival curves (chart 2) in which it may be seen that the mortality for those in group 2 treated medically, if followed for only six months longer (total sixty-six months), becomes approximately 57 per cent, and that for the surgical series the mortality at this time remains unchanged at 60 per cent. Thus, the mortality rate for group 2 may be said to be almost identical in the two series.

Comparison of mortality rates of the two sexes (table 4 B) reveals a higher death incidence among males (93 per cent in the Wagener-Keith control series; 61 per cent in the surgical series) than among females (Wagener-Keith 88 per cent; Peet 42 per cent). It is interesting to note, however, that in groups 3 and 4 there is relatively little difference in the mortality rates according to sex, although here again are clearly seen the significantly lower rates in the surgically treated series.

In charts 1, 2, 3 and 4 we have reproduced separately the survival curves of the four hypertension groups as given by Wagener and Keith. In the same manner we have calculated the survival curves of our patients and present them for comparison with those of the medical control group. The striking differences in these curves becomes at once apparent.

In chart 1 the survival curve for group 1 shows a wide time distribution of the 10 deaths in the control

series, and the straight line is indicative of no deaths in the surgically treated patients (only 4). From such a small number of patients probably no absolutely accurate assumption can be made, but it would appear that operation may well have altered the course in these patients. Without it, according to the control series, one third of them would have been dead within five years.

Comparing the survival curves of group 2, however, one finds that an entirely different situation exists. To these patients with high blood pressures and well defined arteriolar sclerosis without angiospasm of the retinal vessels, operation seems to have offered little or nothing in the way of increasing the survival time. At seventy-two months the two curves meet at 40 per cent. Before this the surgical group has had a definitely lower survival curve. One explanation may be that, of the 9 patients who died in the surgical series, 4 (44.4 per cent) died within the first six months. It is to be considered that the operation might have resulted in a disproportionate percentage of early deaths. Certainly the operation, symptomatic relief being disregarded, seems to have been of little significance in altering the course of the disease.

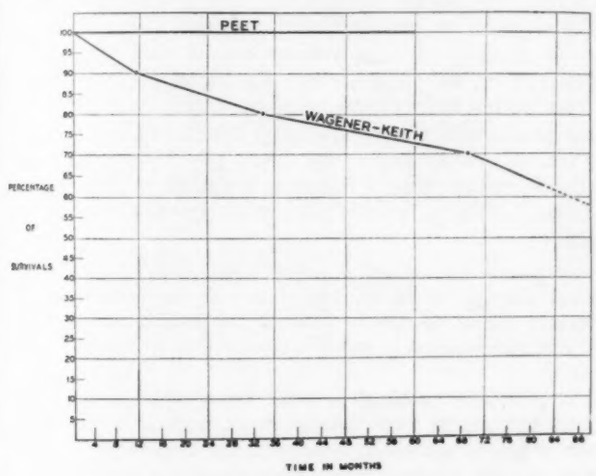


Chart 1.—Comparison of survival curves of group 1.

It is in the study of the survival curves of group 3 that the effects of operation in lessening the mortality of essential hypertension become unmistakably apparent. It should be remembered that in this group the level of the blood pressure is high (average 225 systolic and 134 diastolic); symptoms are present, often very severe; examination of the retinal arterioles reveals unequivocal angiospastic narrowing and, frequently, advanced retinitis with hemorrhages and exudates; renal function may be diminished, and cardiac damage exists in varying degree. It is remarkable, therefore, that the survival percentages of this group, following surgery, are only slightly less than those of group 1 in the control series; they are definitely higher than those of group 2 in both the control and the surgical series and are significantly higher than the comparable group 3 in the control series (57 per cent surgical survivals after five years as against 20 per cent of those patients treated medically).

The evident prolongation of life by operation in this group immediately brings up the question of the comparability of the patients included in the two series. Analysis of the 33 patients in our group 3 shows that 11 patients had fundi which revealed both hemorrhages and exudates, 5 had exudates alone, 7 had hemorrhages alone, 2 had severe angiospasm and evidence of old hemorrhages and exudates, 1 had severe angiospasm and very early papilledema (not considered advanced enough to be placed definitely in group 4), 1 had severe angiospasm and retinal edema and 6 had no other retinal abnormality present at the time of examination than unmistakable and severe angiospasm. In the last

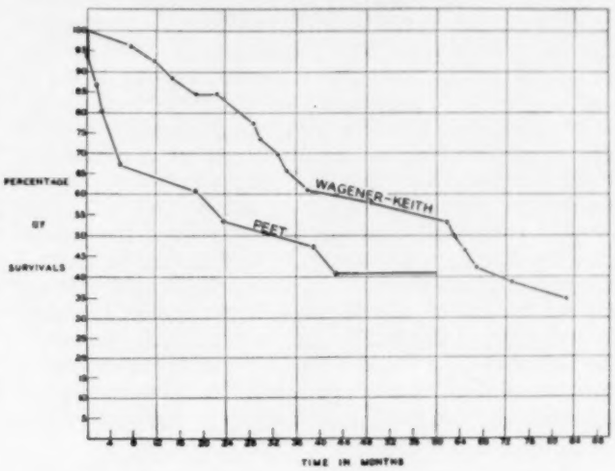


Chart 2.—Comparison of survival curves of group 2.

6 patients mentioned the blood pressure, without exception, was very high (average 220 systolic and 133 diastolic). All complained of severe headaches and other symptoms typical of well defined hypertension. Varying degrees of renal and cardiac damage were present. We have felt that these patients should definitely be included in group 3, since by definition they cannot be included in group 1 or 2 (organic changes of retinal arteriolar sclerosis), or in group 4 (papilledema). Keith and Wagener [4] state that the 6 patients should probably be included in group 3 and that their classification does not define exactly the category into which patients with only unmistakable angiospasm of the retinal arterioles should be placed. We suggest

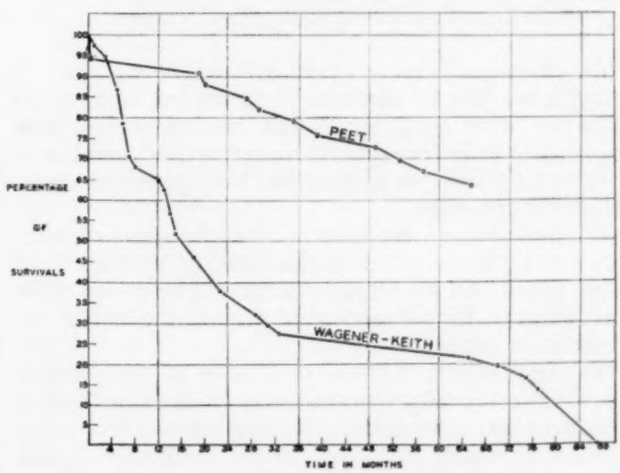


Chart 3.—Comparison of survival curves of group 3.

once again, therefore, that the retinal lesions of hypertension should be classified in four objective groups (group 1, normal fundi; group 2, arteriolar sclerosis without angiospasm; group 3, unmistakable angiospasm with or without varying degrees of arteriolar sclerosis, with or without hemorrhages and exudates; group 4, papilledema).

4. Personal communication to the authors.

With the establishment of the comparability of the two series it may be said that operation has definitely diminished the mortality in this group of patients.

The malignant type of hypertension (group 4) is rapidly fatal. Wagener and Keith state: "The mortality in cases of group IV approaches that found in certain forms of cancer." In their control series 88 per cent of the patients with malignant hypertension were dead within eighteen months. All but 1 patient were dead at the end of five years. In our series of surgically treated patients who had malignant hypertension one half were alive after two years and one third alive after five years. Examination of the survival curves for group 4 reveals that not only are the survival percentages decidedly higher in the surgically treated group as compared with the same group in the control series but also survival is actually higher than in group 3 under medical treatment. It cannot be denied that the surgical treatment of malignant hypertension has definitely decreased the fatality of the disease in our series. The fact that only those patients suitable for operation were included in our series could be presented as an argument against the comparability of the two series.

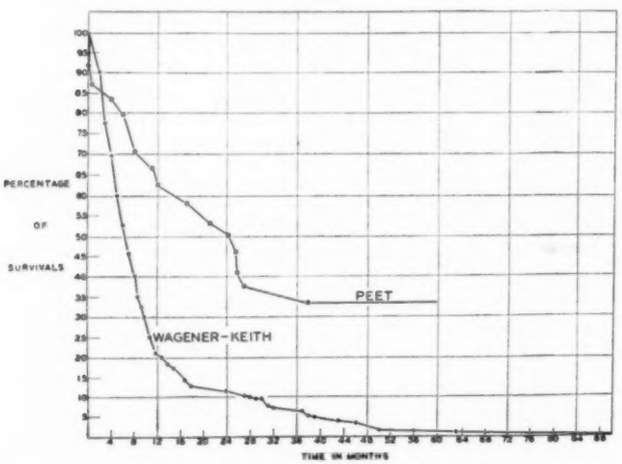


Chart 4.—Comparison of survival curves of group 4.

This objection becomes untenable when the fact is brought out that 98 per cent of the control series (146 patients) were dead at the end of five years. It is implausible to believe that all these patients would have been unacceptable for surgery had they presented themselves for operation.

Confirmation of the fatality of malignant hypertension can be found in the series followed by Page [5] for seven years. Of the 18 patients treated by means other than surgery, 89 per cent were dead at the end of the observation period.

Palmer [6] states: "The severe cases at the younger age [under 45] most frequently are malignant. Medical treatment can offer nothing to stay the rapid progress and can give only brief and partial symptomatic relief. Any possible help from surgery either in halting progress or in real symptomatic relief will be most welcome." The same author writes: "Any real amelioration [of severe hypertension over 45 years of age] by surgical intervention is inconceivable." We offer our statistics in answer to the first statement and in contradiction to the second.

5. Page, I. H.: A Clinical Study of Malignant Hypertension, Ann. Int. Med. **12**: 978-1004, 1939.

6. Palmer, R. S.: The Efficacy of Medical Treatment in Essential Hypertension, New England J. Med. **215**: 569-572, 1936.

BLOOD PRESSURE STATISTICS

Results of treatment in hypertension are most commonly reported in terms of pretherapeutic and post-therapeutic blood pressure values. This type of evaluation, reached without controlled methods and uncorrelated with mortality, renal function, cardiac status, fundus changes and symptomatic relief, is open to criticism because of the considerable variations of blood pressure levels from reading to reading. Ayman [7] states: "Successful therapeutic reduction of blood pressure in essential hypertension may be simulated by many disregarded factors operating on the lability of blood pressure and the hypertensive personality. The failure to control adequately these factors has led to many apparent successes in the past." Ayman considers persistent reduction of at least 30 mm. of mercury systolic as a criterion of drop in blood pressure due to therapy.

We have been fully aware of the difficulty in evaluating therapeutic drops in blood pressure and have attempted to control as carefully as possible our methods of determination. We feel, as already stated, that an objectively measurable factor, such as retinal changes, is the best method of classifying cases of hypertension before operation. Since, however, most authors have presented blood pressure determinations as the method of pretherapeutic and post-therapeutic classification, we shall include the blood pressure levels of our series before and after operation and correlate these levels with the preoperative funduscopic grouping. In our previous paper we have given in detail our methods and criteria of the measurable aspects of hypertension. Briefly, those pertaining to blood pressure include:

The preoperative blood pressure value, which is the arithmetical average of all readings taken in the hospital by all observers before operation. Usually the patients were on bed rest and had previously had a thorough trial of medical treatment.

The postoperative blood pressure value, which is the arithmetical average of four determinations from each arm taken with the patient in a sitting position at the time of his entry into the office. Any readings taken independently by other observers were also included. These patients were almost invariably ambulatory and were in the midst of rigorous check-up examinations by the various departments of the University Hospital Clinic.

In general, it could be said that the preoperative blood pressures were determined under conditions optimum for a low level and the postoperative pressures under conditions conducive to a high level. This would seem to make the criteria given here definitely valid.

A drop of 40 mm. of mercury systolic and 15 mm. diastolic or more from the preoperative level is considered a significant reduction in blood pressure. No pressure is considered significantly reduced unless both systolic and diastolic values are lowered the stated amount.

A drop of 80 mm. systolic and 25 mm. diastolic or more is considered a decided reduction in blood pressure. Both systolic and diastolic values must be lowered the stated amount.

A drop to, or lower than, 130 mm. systolic and 90 mm. diastolic for patients up to the age of 40 is considered a reduction of blood pressure to "normal." After the age of 40 the drop must be to, or lower than,

7. Ayman, David: The Evaluation of Therapeutic Results in Essential Hypertension, J. A. M. A. **96**: 2091-2094 (June 20) 1931.

150 mm. systolic and 100 mm. diastolic. Both systolic and diastolic values must be lowered the stated amount.

A rise of 10 mm. systolic and 5 mm. diastolic is considered an increase in blood pressure. Both systolic and diastolic values must be raised the stated amount.

In order to eliminate a mere temporary drop in blood pressure following a major operative procedure, no postoperative result was considered unless at least nine months or more had elapsed since the time of operation.

Table 6 demonstrates that the preoperative blood pressure level in each group was higher than that in the preceding group and that the levels, especially in groups 3 and 4, were very high.

TABLE 6.—*Preoperative Blood Pressure Averages (Correlated with Keith Hypertension Grouping)*

Preoperative Keith Hypertension Grouping	Preoperative Blood Pressure Averages
1	191/115
2	217/131
3	225/134
4	227/148

In table 7 are presented the postoperative results in 60 cases studied at least once nine months or more postoperatively. It is of great significance to note that those cases presenting the highest blood pressures and the retinal changes of papilledema or angiospastic retinitis (groups 4 and 3) are those in which the greatest benefit from surgery was derived. In fact, both groups show a percentage of cases presenting reduced pressures twice that of group 2. It should not be overlooked that only 6 per cent of the cases showed an increase in blood pressure following operation.

In our previous paper, presenting statistics on 350 patients, the percentage with reduced blood pressure nine months or more postoperatively was 51.4, as against 42 for this smaller series. We suggest that this difference may be due to the fact that many of our earlier patients were operated on who would not now be considered candidates for surgery. We have also shown in the statistics of our larger series that the reduction of blood pressure is maintained throughout the postoperative years. Many patients in the present series did not present themselves for their first check-up study for several years after operation. No selection of patients has been made since; of the 16 patients not considered in table 7, 15 were dead within nine months and only 1 failed to return for check-up.

TABLE 7.—*Postoperative Blood Pressures (Correlated with Preoperative Keith Hypertension Group)*

Preoperative Keith Hypertension Group	Total Cases Studied Postoperatively (9 Mos. or Later)	Reduced	Unchanged	Increased
1	4	1 (25%)	3 (75%)	0
2	9	2 (22%)	7 (78%)	0
3	31	15 (48%)	14 (45%)	2 (7%)
4	16	7 (44%)	7 (44%)	2 (12%)
Totals	60	25 (42%)	31 (52%)	4 (6%)

Table 8 is included in order to demonstrate that the postoperative reduction in blood pressures is not minimal. It should be noted that 43 per cent of the patients with reduced pressure either had pressures reduced to normal or markedly reduced. In our larger series the percentage is 48, the difference again probably being due to our early acceptance of patients who, in later years, were not considered fit candidates for surgery.

In addition to the definite results obtained by surgery in reducing blood pressure, it is of significance to note the effect on the ocular fundi. Of 12 patients in group 4 preoperatively (papilledema with malignant hypertension) and followed nine months or more postoperatively, all showed improvement in the retinal changes; 9 of the 12 had complete disappearance of the papilledema. Of 26 patients in group 3, 69 per cent showed postoperative improvement in the retinal lesions, 27 per cent were unchanged and 4 per cent were worse. Of 8 patients in group 2, 4 were improved and 4 were unchanged. The 4 patients in group 1 remained unchanged following operation.

Operative treatment in this series, as in our larger series, resulted in improvement in symptoms and incapacitation. Thus, of the 15 patients in group 4 on whom data were obtained nine months or more postoperatively, 6 became completely free of symptoms and 8 were partially improved. Eight patients who were partially or completely incapacitated before operation returned to full time work postoperatively. Two showed partial improvement in their incapacitation. There were none whose symptoms or incapacitation grew worse.

TABLE 8.—*Analysis of Patients with Reduced Blood Pressure (Correlated with Preoperative Keith Hypertension Grouping)*

Preoperative Keith Hypertension Group	Total Patients with Reduced Pressure (9 Mos. or More Postoperative)	Reduced to Normal (130/90 for Ages 20 to 40; 150/100 for Ages 40 to 60)	Markedly Reduced (More than 80 Mm. Systolic and 25 Mm. Diastolic)	Reduced (But Not to Normal or Markedly)
1	1	1	..	..
2	2	..	..	2
3	15	4	1	10
4	7	2	3	2
Totals	25	7 (27%)	4 (16%)	14 (56%)

In group 3 data on postoperative symptoms and incapacitation were obtained on 31 patients. Thirteen became symptom free and 16 returned to full time work, having been totally or partially incapacitated before operation. Fourteen showed partial improvement in symptoms and 4 partial relief of incapacitation. No patient had more severe symptoms following operation. Only 1 became more incapacitated.

In group 2 (9 patients studied) 4 became symptom free and 4 showed partial improvement. Five returned to full time employment and 3 had partial relief of their incapacitation. None became worse.

Of the 4 patients in group 1 none developed symptoms, 2 returned to full time work, 1 was partially relieved of incapacitation and 1 became partially incapacitated.

Because of incomplete studies made in some of the early cases presented in this series no conclusive statistics on improvement in renal and cardiac function are presented. It is to be expected, however, that, in general, results would be the same as in the study of 350 cases, i. e. heart size diminished in 64 per cent, improvement in electrocardiogram in 53 per cent, improvement in urea clearance in 52 per cent and improvement in urine concentration in 45 per cent. We shall present a correlation between funduscopic observations and renal function in a future paper.

COMMENT

Search through the voluminous literature on the treatment of hypertension has failed to yield studies which, like those of Wagener and Keith, can be compared accurately with ours. This failure is usually due to lack of precise classification of the cases, inadequacy of post-therapeutic time of observation and lack of mortality statistics.

Most observers in the field of hypertension, however, agree that persons under 50 years of age with a high level of blood pressure, severe symptoms, definite organic damage resulting in retinal changes and decreased renal and cardiac function respond poorly to treatment. Patients with malignant hypertension are regarded as hopeless.

Blackford, Bowers and Baker [8] state: "We have no instance in which continued observation has shown any constant normal blood pressure after a reading above 175 has been made at first examination." Palmer and Thorp [9] have stressed the severity and rapid fatality in younger patients (under 45 years) with the severe and malignant types of hypertension. Keith, Wagener and Kernohan [10] in 1928 described the syndrome of malignant hypertension characteristically marked by a rapidly fatal outcome. Page,[11] Ellis,[12] Murphy and Grill [13] and others have amply confirmed this.

The less severe forms of essential hypertension respond to various methods of therapy in respect to both symptomatology and reduction in blood pressure. Ayman [14] analyzed thirty-five articles in all of which symptomatic relief, reduction in blood pressure or both are claimed. Psychotherapy,[15] potassium sulfocyanate [16] and reduction of weight with sedation all have ardent adherents. In none of the articles dealing with these methods, however, were we able to find comparable mortality statistics over an extended period of years. Few described results which were maintained over an adequate post-therapeutic period, nor was an exact definition given of what were considered "good" results.

The surgical treatment of hypertension has been reported by various workers: Crile,[17] Smithwick,[18] Page and Heuer,[19] Peet, Woods and Braden,[1] and Allen and Adson.[20] As yet no extended study of mortality has been presented. All state that there is reduction in blood pressure and symptomatic relief.

Rytand and Holman [21] have reported results on 40 hypertensive patients following bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. These results are not comparable to those in our series, since the authors state that they have ignored the usual criteria for selection of patients. Thus, of the 34 patients who either died or failed to have a drop in blood pressure following operation, 24 (70 per cent) had elevated blood ureas ranging from 25 to 80 and would, consequently, have been considered unfit for operation in our clinic. The 6 patients whose blood pressures were reduced all had normal preoperative blood ureas. Thus these authors contribute mainly confirmation of the fact that patients with definitely elevated blood nonprotein nitrogen levels (or blood urea) should not be operated on.

Allen and Adson, in their five year study of 224 patients on whom bilateral subdiaphragmatic resection of the splanchnic nerves was performed, with resection of the celiac ganglion and resection of the lumbar sympathetic trunk, including the first and second lumbar ganglions, state: "Rapidly progressive hypertension seems to respond less favorably than slowly progressive hypertension does. Generally, patients with very high blood pressures (220 systolic and 130 diastolic or more, expressed in millimeters of mercury) respond unfavorably to sympathectomy." This has not been our experience, as shown by the statistics presented and by the fact that the average preoperative blood pressure of our 350 patients previously reported on was 218 systolic and 133 diastolic and of this series of 76 patients was 225 systolic and 137 diastolic. Of our group 3 the level averaged 225/134, and of group 4, 227/148. Also, these authors report blood pressure results in 74 per cent of group 3 and 100 per cent in group 4 as "temporary or poor." Their best results are in group 2, the group in which our poorest results were obtained. No analysis of mortality statistics is given.

Elsewhere Allen and Adson [22] state: "Surgical treatment is advisable for patients who have hypertension, group 2 and group 3, if the hypertension is known to be progressive, if the function of the heart and kidneys is good and if the value of the blood pressures become normal or approximately normal as a result of rest or sleep, or following the intravenous injection of pentothal sodium, or following the administration of sodium amytal or the nitrites. Hypertension, group 4, does not respond satisfactorily to surgical treatment." It becomes obvious from these statements that the results in the study of Allen and Adson are not directly comparable to those in our series because of the lower average blood pressure levels and the lesser severity of retinal changes in their cases.

On critical reexamination of the statistics presented in this study several important facts relative to the treatment of essential and malignant hypertension come to light. Foremost among these is the fact that bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy (apparently alone of all reported methods of treatment) offers hope of prolonged survival to persons suffering from malignant hypertension (1 out of every 3 patients survived five years or longer). In addition, patients with a very high level of blood pressure, angiospastic retinitis, severe

8. Blackford, J. M.; Bowers, J. M., and Baker, J. W.: Follow-Up Study of Hypertension, J. A. M. A. **94**: 328-333 (Feb. 1) 1930.

9. Palmer, R. S., and Thorp, E. G.: Clinical Considerations in Regard to Etiology, Characteristics, and Prognosis in Essential Hypertension at Different Ages, New England J. Med. **214**: 1019-1022, 1936.

10. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**: 141-188 (Feb.) 1928.

11. Page, I. H.: A Clinical Study of Malignant Hypertension, Ann. Int. Med. **12**: 978-1004, 1939.

12. Ellis, A.: Malignant Hypertension, Lancet **1**: 977-980, 1938.

13. Murphy, F. D., and Grill, John: So-Called Malignant Hypertension: A Clinical and Morphologic Study, Arch. Int. Med. **46**: 75-104 (July) 1930.

14. Ayman, David: An Evaluation of Therapeutic Results in Essential Hypertension, J. A. M. A. **95**: 246-249 (July 26) 1930.

15. Robinson, S. K.: A Comparison of the Medical and Surgical Treatment in Hypertension with Special Reference to the Importance of Psychic Factors in Evaluating the Results with a Report of Ninety-Two Cases Treated Medically, J. Nerv. & Ment. Dis. **91**: 157-174, 1940. Ayman.[14]

16. Davis, Loyal, and Barker, M. H.: Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, Ann. Surg. **110**: 1016-1036, 1939.

17. Crile, George: The Surgical Treatment of Hypertension, Philadelphia, W. B. Saunders Company, 1938.

18. Smithwick, R. H.: A Technic for Splanchnic Resection for Hypertension, Surgery **7**: 1-8, 1940.

19. Page, I. H., and Heuer, G. J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, Arch. Int. Med. **59**: 245-298 (Feb.) 1937.

20. Allen, E. V., and Adson, A. W.: The Treatment of Hypertension: Medical Versus Surgical, Ann. Int. Med. **14**: 288-307, 1940.

21. Rytand, D. A., and Holman, Emile: Arterial Hypertension and Section of the Splanchnic Nerves, Arch. Int. Med. **67**: 1-24 (Jan.) 1941.

22. Allen, E. V., and Adson, A. W., cited by Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**: 317-430, 1939.

symptoms and a definite decrease in renal and cardiac function also are given a considerably better prognosis than has heretofore been demonstrated. Patients with retinal arteriolar sclerosis, however, seem to survive, after operation, no longer than those treated medically.

It would seem, then, that patients with essential hypertension fall logically into four distinct groups based on funduscopic observations alone: those with normal fundi (proposed group 1); those with retinal arteriolar sclerosis (proposed group 2); those with definite angiospasm plus varying degrees of arteriolar sclerosis (proposed group 3), and those with papilledema (proposed group 4). Within each of the last three groups the cases may be subdivided into degrees of severity, i. e. minimal, moderate, marked or severe. This classification has the advantage that it is reached objectively from examination of the ocular fundi and does not include such variables as symptoms, level of the blood pressure and degree of organic damage.

The ultimate prognosis in terms of survival is best (aside from those with normal fundi) for those showing retinal arteriolar sclerosis when treated medically (our group 2, Keith groups 1 and 2). With surgery, however, the ultimate prognosis for those with retinal arteriolar angiospasm (our group 3, Keith group 3) becomes better than that for the above group, and the patients with papilledema (our group 4, Keith group 4, those with malignant hypertension) are removed from the category of "hopeless." The definitely better relative prognosis in the two latter groups following operation would seem probably to depend on the fact that angiospasm, with or without papilledema, indicates a physiologic process which is reversible by the operation not only in the arterioles of the ocular fundus but also on the arterioles elsewhere in the body.

Theoretically, the effects of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy could depend on a release of angiospasm in the kidneys of patients with essential hypertension by interruption of the sympathetic outflow to the renal vessels. The work of Goldblatt and many others has shown that renal ischemia in the experimental animal can produce hypertension which is practically identical with essential or malignant hypertension in man. This hypertension would seem to be due to a circulating pressor substance elaborated by the ischemic kidney. It is logical to suppose that, if angiospasm in the human kidney could be released, the resultant relief of the renal ischemia should decrease or abolish the production of the pressor substance. Our good results in patients with retinal angiospasm and our poorer results in those with arteriolar sclerosis lend credence to the theory of relief of renal ischemia as a basis for the operative treatment of hypertension since, most probably, the angiospasm in the kidney can be relieved whereas sclerosis represents an irreversible process.

The proof of this theory would seem to depend on the demonstration of renal ischemia in hypertensive patients and its relief in those successfully treated. In the laboratory of the Neurosurgical Service at the University Hospital (in conjunction with Dr. Piero Foa) we have tentatively corroborated the work of Smith [23] showing the presence of renal ischemia in patients with hypertension by means of diodrast and inulin clearances. By means of follow-up studies we hope to demonstrate the presence or absence of any increase in renal blood flow following operation and its correlation with clinical results.

It is our impression, therefore, that funduscopic observations are of definite aid in the prognosis of the patient with essential hypertension presenting himself for operation. If angiospasm of the retinal arterioles is present alone, we feel that his prognosis, regardless of the level of blood pressure, is fairly good following operation and that it becomes less favorable as the degree of arteriolar sclerosis accompanying the angiospasm increases. This is true also in regard to the patient with the papilledema of malignant hypertension, which would seem to indicate a high degree of the angiospastic process, its reversibility depending on the degree of arteriolar sclerosis present. The patient with either primary (as seen usually in older patients) or complete postangiospastic retinal arteriolar sclerosis has much less to gain in terms of ultimate prognosis from the operation.

In this paper we have not emphasized symptomatic relief following operation. In certain instances we feel that the operation is justifiable regardless of the ultimate prognosis because of the definite symptomatic relief obtained in about 85 per cent of the patients operated on.

SUMMARY

Seventy-six consecutive patients with essential and malignant hypertension were operated on by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy and were followed for from five to seven years.

All cases were classified preoperatively according to the four groups suggested by Keith, based on retinal changes.

Mortality statistics of each group over the five to seven year period are compared with a similarly classified control group treated medically and described by Wagener and Keith.

Statistical results of operation are also presented in regard to blood pressure reduction, retinal changes and relief of symptoms and incapacitation following operation.

Patients with essential hypertension should be classified into four groups according to ocular fundus findings: group 1, normal fundi; group 2, arteriolar sclerosis without angiospasm; group 3, unmistakable angiospasm with or without varying degrees of arteriolar sclerosis, with or without hemorrhages and exudates; group 4, papilledema.

CONCLUSIONS

1. The prognosis of patients with a high level of blood pressure and angiospastic changes of the retinal arterioles is much more favorable following operation than following medical treatment.

2. The surgical treatment of patients with malignant hypertension has resulted in a survival of 33 per cent after five years, whereas following medical treatment in the control series the mortality was more than 99 per cent.

3. In general, a favorable prognosis following operation seems to depend on a minimal degree of retinal arteriolar sclerosis rather than on the level of blood pressure, or the absence of retinitis with hemorrhages and exudates, or papilledema.

23. Smith, H. W.; Goldring, W.; Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man, with Special Reference to Essential Hypertension, Am. J. Physiol. **123**: 189-190, 1938. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow and Functional Excretory Mass in Essential Hypertension, J. Clin. Investigation **17**: 505, 1938.

DOUBLE UTERUS WITH PREGNANCY

GOODRICH C. SCHAUFFLER, M.D.
PORTLAND, ORE.

In the last six years I have seen 11 patients [1] with more or less complete duplex anomalies of the uterovaginal tract, each of whom has had one or more pregnancies (a total of thirty-two). The present discussion applies strictly to the association of the two conditions; no attempt is made to present embryologic or purely gynecologic considerations, and my approach is from the clinical rather than from the academic side.

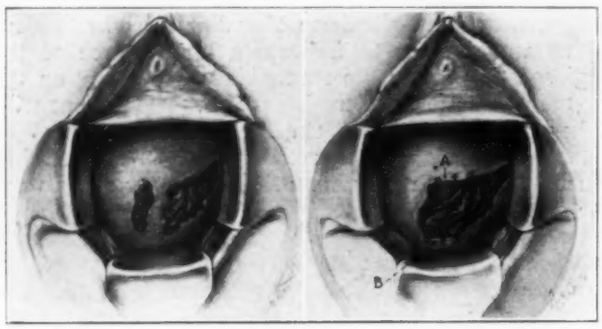


Fig. 1 (case 10).—Left, septate double cervix with rudimentary double uterus; the cervical anomaly is visible—distended in front of the descending head; right, the septum *A* to *B* has been excised as indicated.

Briefly, duplex anomalies of the uterovaginal tract are due to (1) irregularities of fusion involving the normal junction of the müllerian ducts to form the symmetrical halves of the corpus of the uterus and (2) irregularities in canalization involving the urogenital sinus or lower uterine and vaginal tracts. The most common anomaly is simple uterus arcuatus, departing little from the normal contours and hence not as often important clinically. I have not included such cases.

The misfortunes that occur to these patients may too often be laid directly at the gynecologist's door. A single case report will illustrate:

CASE 7.—An attractive healthy girl with a definitely limited intelligence had a vaginal septum removed at the age of 19, at which time there was a clinical notation made of two cervical openings. She immediately became pregnant and was delivered by a physician who did not recognize the anomaly. From this time on to the present she has been treated by nine physicians. She has had two healthy children at term; she has had extramarital gonorrhea with pelvic involvement; she has had two pelvic laparotomies and one miscarriage at five months; she is now a prostitute of the better class.

I have collected the complete records in this unusual case. More incorrect than correct diagnoses were made by the nine physicians. She was unnecessarily pounded, thumped, curetted, aborted and laparotomized, mainly because of a complete double uterus which presented diagnostic difficulties during pregnancy.

Duplex anomalies of the uterus and even of the vagina are seldom brought to the patient's attention prior to complete sexual activity. Menstrual disturbances are not infrequent and, requiring examination, may call attention to such conditions. Resultant hematometra is a rare occurrence and hematocolpos has been noted. On the other hand, duplex anomalies are frequently not noted until intercourse is begun, and occasionally not then. Out of 5 patients with double vagina in this series only 2 were aware of the duplex anomaly prior to examination by a physician. In 1 instance, to be sure, the husband had made the discovery and stated that the available functional variant was a definite asset to his marital relations. This is certainly a rare instance, one might almost say, of legal polygamy.

Frequently neither the onset of menstruation nor marriage calls attention to the double uterus. Unexplained abortion or miscarriage often leads to its discovery. Although a few of these patients may have difficulty in becoming pregnant (cases 5 and 6), my experience in general coincides with that of Norman Miller,[2] Falls [3] and Findley [4] to the effect that fertility is definitely not impaired. In fact, one is almost tempted to infer that fertility and the sex urge are distributed among these women in the same generous ratio as their organic sex equipment.

In the group of 11 patients there were thirty-two pregnancies, of which seventeen (53 per cent) resulted in abortion or miscarriage. Reasons for the frequency of spontaneous abortion and miscarriage seem fairly obvious. Intrauterine septums and irregularities of the fundus are poorly vascularized, the musculature is thin and irregularly disposed and the stroma is inadequate.

Uterine inertia, occasionally serious, is described as a common occurrence at labor. In fifteen deliveries in our group, however, it was noted only three times. Mechanical disarrangement of muscle fibers logically results in dysfunction of uterine muscle action. Expulsive force may be insufficient to effect delivery. More often, the chief difficulty involves failure in the mechanism of cervical dilation. I have observed almost the entire function of dilation in a double cervix. Figures 1 and 2 (case 10) illustrate the condition noted at the first vaginal examination shortly after the onset of labor. The septum *A-B* was removed at this time and the anomaly clearly outlined. The cervix from then on was watched or palpated almost constantly throughout the remainder of the labor. There was no other obvious reason for dystocia, yet this labor was exceedingly tedious. Even when the head was finally forcibly pushed into the cervix by the fundic musculature, one sensed a fault or slowness in the mechanism of cervical effacement and dilatation. Following delivery, the cervix was repaired as indicated in figure 2. Now, three months post partum, the patient has a fairly normal appearing cervix.

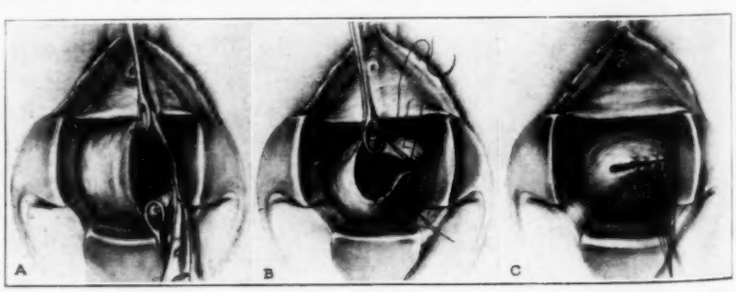


Fig. 2 (case 10).—*A*, excision of the septum created a single, irregular cervical orifice. After delivery the edges to the left were freshened and (*B* and *C*) sutured to form a single, normal appearing cervical opening.

Read before the Section on Obstetrics and Gynecology at the Ninety-Second Annual Session of the American Medical Association, Cleveland, June 6, 1941.

1. Seven in my practice, 4 in the Department of Obstetrics and Gynecology, University of Oregon Medical School and Multnomah County Hospital.

2. Miller, N. F.: Am. J. Obst. & Gynec. **4**: 398 (Oct.) 1922.
3. Falls, F. H.: Am. J. Obst. & Gynec. **15**: 399 (March) 1928.
4. Findley, Palmer: Am. J. Obst. & Gynec. **12**: 318 (Sept.) 1926.

Weakness or dangerous irregularity of the uterine wall may be present. Rupture of the uterus has occurred, but not frequently. It did not occur in our series. The pregnant horn may be expected to be embarrassed by the nonpregnant horn, pretty much as it might be by a subserous fibroid or other intimately attached growth. My experience, and that of most careful observers, indicates that the nonpregnant horn itself is not responsible for radical complications as often as one might expect. Occasionally it is retained in the pelvis, swings posteriorly and becomes a source of serious dystocia. Rarely it is twisted or incarcerated and may necessitate radical intervention. Frequently it contributes to fundic irregularities which are responsible for malposition of the fetus. The latter complications, however, are recognizable and their dangers may generally be circumvented. Out of fifteen deliveries, four

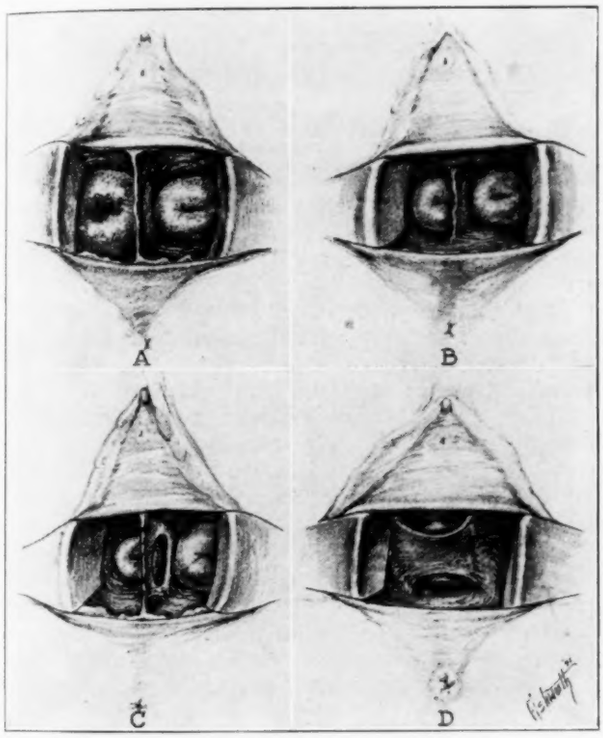


Fig. 3.—Types of vaginal septums noted in our patients: *A*, typical complete midline vaginal septum with double cervix and uterus (case 6). *B*, partial midline septum with double cervix and double uterus (case 5). *C*, midline septum with fenestra, double cervix and double uterus (case 2). *D*, partial transverse or oblique septum with single cervix and double uterus (case 8).

were breech, all with satisfactory outcome. In 2 patients (cases 9 and 11), 1 now under observation, I have been able to follow meticulously the disposal of the nonpregnant horn by abdominal and vaginal examinations. In both instances it has been carried well out of harm's way by the sixth month. Others state that, even though it remains deep in the pelvis, it may not necessarily cause absolute dystocia or serious harm. Such danger, however, exists and is to be kept constantly in mind.

The physiology of the nonpregnant horn is of interest. Its changes are in most respects similar to those which occur in the uterus itself during ectopic pregnancy. Its actual enlargement is described variously as from twice to three times its normal size. I have examined such uteri in 5 instances (cases 2, 9 [twice], 10 and 11) at between four and eight months. I do not believe that the accessory uterus often more than doubles its actual size. In 1 instance its enlargement was scarcely appreciable at three months.

Decidua is laid down in the nonpregnant horn. It is more nearly normal and therefore considerably greater

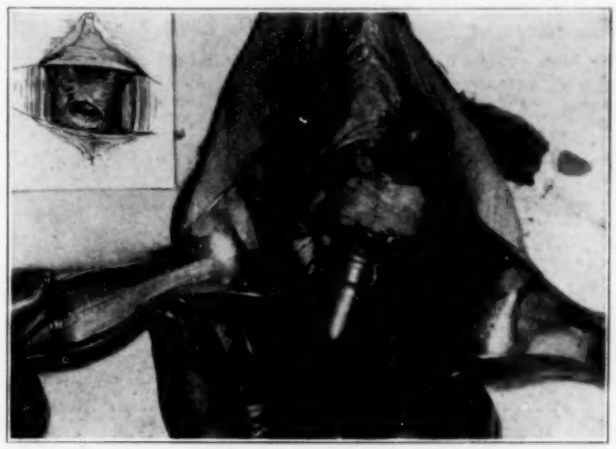


Fig. 4 (case 8).—Appearance of partial transverse or oblique septum as drawn in figure 3 *D*. The inset clarifies the condition.

in total volume than that ordinarily laid down in ectopic pregnancy. This point is important in relation to the problem of its expulsion post partum, which is occasionally serious. I believe that it is important to realize that this decidua is subject to the same hormonal influences which control the actual pregnancy. Such a uterus, then, may not be expected to bleed normally at any time during the pregnancy. When irregular

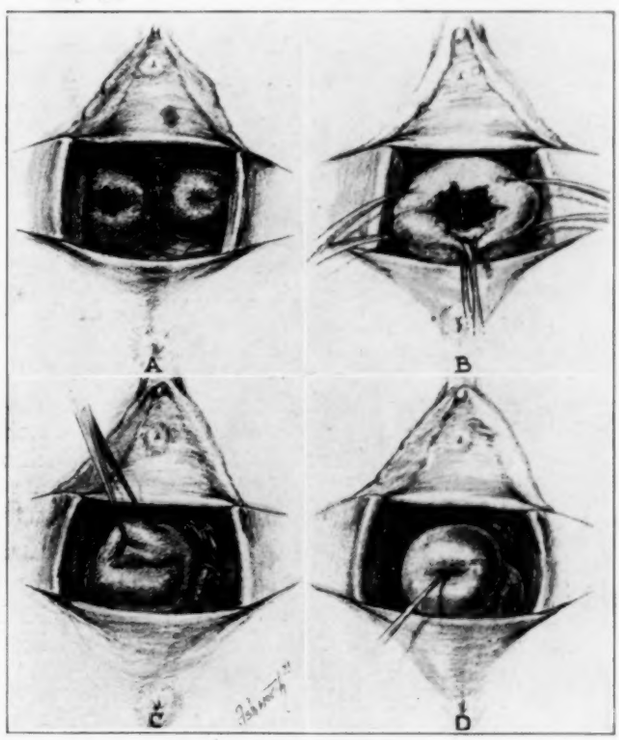


Fig. 5.—*A*, typical double cervix with double uterus. The remains of the excised vaginal septum are visible between the two cervices (case 6). *B*, single wide transverse external os with complete double uterus above. Uterine septum visible at level of internal os (case 8). *C*, two obliquely placed cervical openings with double uterus (case 10). *D*, obliquely placed cervical openings with single uterus. Curved sounds passed in the right and out the left cervical opening (case 4).

bleeding occurs, it should be considered as reflecting damage to the chorionic tissue of the pregnancy itself and should call for the same measures indicated by any

threatened abortion. It occurred three times in fifteen successful pregnancies in this group and consistently in those who miscarried.

DIAGNOSIS

History.—Too often both the patient and her physician may not appreciate the presence of double uterus or even of double vagina. Early diagnosis of double uterus was missed more often than it was made in our series. Diagnostic points in the history will be mainly by inference. Menstrual irregularities are not uncommon and dyspareunia is occasionally a symptom. It should be recalled that repeated unexplained abortion or miscarriage is to be suspected. It is a mistake to regard a history of normal pregnancy and delivery as excluding the diagnosis. Unexplained repeated breech or transverse position may also be suggestive. Bleeding during pregnancy is named by some as characteristic. It has not been so in this series and, in any event, should not be regarded as a casual symptom.

Physical Examination.—Patients even with the complete anomaly seldom show external stigmas. Vaginal septums are of many varieties and may easily be misinterpreted as artefacts resulting from previous childbirth trauma. The remains of vaginal septums are particularly likely to be misinterpreted in this way. Almost any sort of septal anomaly may occur. Those which I have seen are illustrated in figure 3. It should be noted that the septum is by no means always the typical midline anteroposterior type and is often incomplete. Any notable irregularity of the vaginal wall

Fig. 6 (case 6).—The uterosalpingogram shows double cervix and double uterus with normal patent tubes. Inset clarifies the condition. The window between the two uteri allowed the escape of iodized poppy seed oil back into the vagina until the left cervix was plugged. A satisfactory picture was then obtained. Inset indicates how this diagnosis was made by sound prior to injection of the iodized oil.

should suggest the possibility of double anomaly elsewhere in the tract.

Double cervix is often first suggested by a vaginal anomaly and should be easily recognized. The typical bilateral anomaly is illustrated in figure 5*A* (case 6) but is by no means always present. The two cervices in some instances may be obliquely placed, as occurred in 2 of the cases (figs. 5*B* and *C*). Again there may be a single comparatively free cervical opening, the cervical and uterine septum beginning within the external

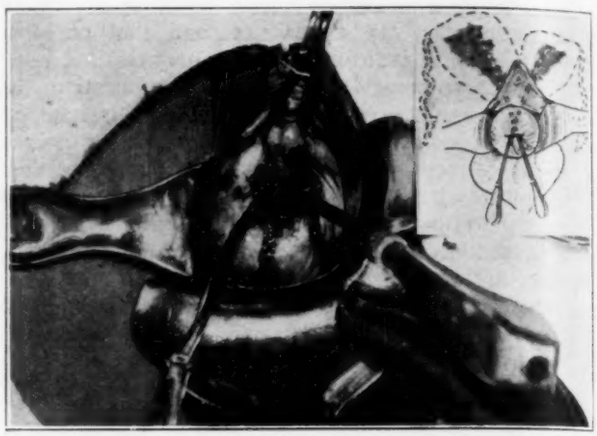


Fig. 7 (case 8).—A single cervix with complete double uterus (see also figure 3*D*). The sounds passed through a single cervical canal, crossed and separated widely at a septum which could be clearly delineated and entered widely separated uterine horns, as indicated in the inset. Oil escaped so freely that the tubes could not be filled.

os as in case 8 (figs. 5*B* and 7). Such a condition may be mistaken for cervical distortion due to childbirth tears.

Metal sounds, while they cannot be used in pregnancy, are of the greatest assistance in enabling one to gain a correct concept of the actual situation within the cervix and uterus. In case 4, for example (fig. 5*D*), a sharply curved sound passed into one external os could be brought out at the other external os. In case 6 (fig. 6), sounds passed into the two uteri through cervices side by side were felt to click together clearly about an inch and one-half within. In case 8 (figs. 7, 9 and 5*B*), sounds passed through a single cervix crossed and separated widely at a septum which could be clearly delineated and entered widely separated uterine horns, as indicated in the inset. Such information is helpful and easy to obtain.

Unfortunately, simple bimanual pelvic examination is not apt to clarify the situation in the absence of other suggestive manifestations in the lower tract. In pregnancy any tumor attached to the uterus and rapidly increasing in size should be suspected. Ectopic pregnancy may be difficult to exclude, but other unexplained tumors associated with pregnancy are not frequently to be confused.

Uterosalpingograms yield the most complete information but are not advisable in cases of pregnancy or if adnexal infection is to be differentiated. The injection of iodized oil frequently presents some technical difficulties but has offered invaluable information. The procedure was done seven times in this study, and the resulting roentgenograms are those presented in the illustrations. Figure 8 illustrates the appearance found in case 5 in which an ectopic tubal pregnancy was removed with the right tube. Figure 9 (case 8) illustrates a double uterus in a patient with polypoid endometriosis. She had had two normal children and three miscarriages. Both uteri were curetted and showed similar endometriums.

Management.—The first consideration involves the advisability of allowing or advising patients with frank anomalies of this sort to become pregnant. It should

be recalled that fertility is generally high but that the incidence of abortion and miscarriage is also high. With reference to complete double uterus, the usual concern felt in relation to abortion or miscarriage is definitely increased by the possibility of harm from the nonpregnant uterus. The 11 patients whom I have seen have had seventeen abortions and miscarriages, none with serious permanent harm. They have had fifteen pregnancies successfully terminated. My experience then substantiates the opinion of Falls, Miller and Findley and others that if the patient is willing to assume the additional dangers of pregnancy under such circumstances she should be allowed to. Naturally, patients who have already delivered successfully should not be denied subsequent pregnancies—at least one or perhaps two.

Elective operative sterilization should be justified only by serious results from past pregnancies or other pathologic conditions which indicate the operation. There is seldom a correct indication to remove an accessory uterine horn—at least in the interest of later pregnancies, and pregnancy in such a crippled uterus should be considered precarious. The advisability of obliterating an intrauterine septum by excision or electrosurgery is questionable.

In the care of the pregnancy unusual precautions should be observed against the tendency to frequent abortion or miscarriage. Beside the usual precautions, wheat germ oil derivatives and progesterone may be indicated. The occurrence of bleeding and especially of bleeding with cramps is never to be regarded as harmless because it may be thought to originate in the accessory uterus.

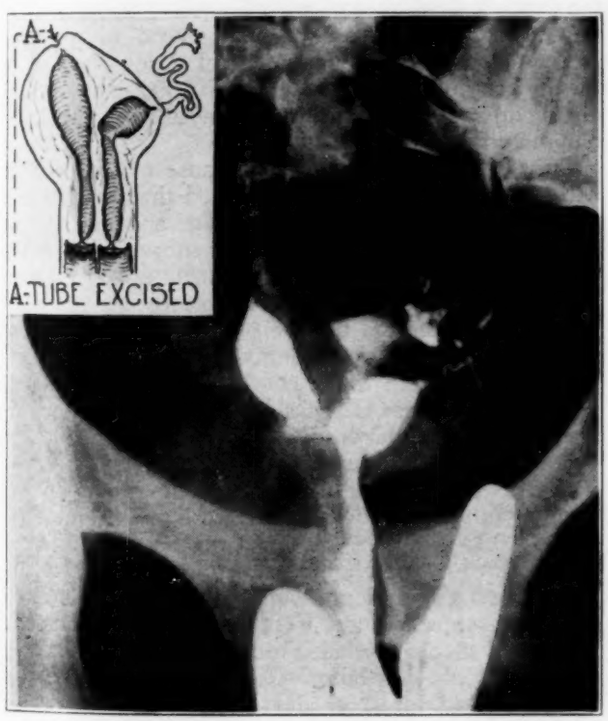


Fig. 8 (case 5).—The uterosalpingogram shows a complete double uterus six weeks after an ectopic pregnancy in the right tube had been removed. The right tube is absent, the left tube filled. These uteri had to be injected one after another in very rapid sequence to obtain a satisfactory picture.

In the later months of pregnancy the uterus should be kept under the most careful surveillance. Malpositions of the fetus due to irregularities of contour of the fundus are frequent. Also, it is important to follow the location and general characteristics of the accessory uterine horn, if possible. If it is recognized early in pregnancy, it can frequently be identified throughout, especially if it threatens to be a dystocic factor because of its deep pelvic station.

Fig. 9 (case 8).—Double uterus with single cervix in a patient with polypoid endometriosis who had had two normal pregnancies and deliveries and two miscarriages. Similar curettings were obtained from the two uteri (see also figures 3 *D* and 7).

During labor the possibility of weakened uterine musculature should be constantly borne in mind—the patient being hospitalized at once when contractions begin. Preparation for section, particularly in the case of a first delivery, should be complete.

Operative equipment should be available for the plastic management of vaginal and cervical anomalies. Their management is seldom described as complicated and has not been so in my experience. These anomalies are most often clearly delineated early in labor and in general may be easily dealt with—most often by simple excision of the septums. The time to do this is when the descending fetus has clearly delineated the actual necessity. At such a time the cervix will be thinned out and relatively avascular, and the necessary attention to the vagina will be visible and obvious. In general, no great concern need be felt in this connection. Should serious complications arise suddenly, cesarean section should be an available recourse.

Difficulties in the third stage should be anticipated but frequently do not occur. An adherent placenta caused by infarct or an unsatisfactory basalis may present difficulties. Hemorrhage may occur from this source and also from uterine inertia resulting in retarded involution. Occasionally disposal of the heavy decidua from the accessory uterus may create a definite complication in the early puerperium. Such difficulties have not been prominent in the labor records of my patients.

SUMMARY

1. In the last six years 11 patients with duplex anomalies of the uterovaginal tract have been seen. Each has had one or more pregnancies—a total of thirty-two.

2. Failure to diagnose these conditions often results in harm to the pregnant patient. Helpful diagnostic points may be menstrual irregularity, dyspareunia, repeated unexplained abortion or miscarriage and repeated malposition of the fetus. Bleeding during pregnancy is not to be regarded as a casual symptom.

3. The use of two uterine sounds is most helpful in diagnosis. Uterosalpingograms yield the most complete information available. Six of my patients were so studied (roentgenograms are shown).

4. Fertility in this group is high, but miscarriage and abortion are also frequent. Our 11 patients had thirty-two pregnancies—with seventeen abortions (53 per cent). Most patients may be allowed to become pregnant but must be made to understand the potential difficulties. Efforts to correct such conditions by surgery in the interest of later pregnancy are of doubtful validity.

5. Care of the pregnancy demands general and special measures to strengthen and protect the ovular attachment. The progress of the nonpregnant horn is to be followed as carefully as possible. My experience in this connection has been of interest.

6. At delivery, operative equipment for the management of vaginal and cervical anomalies, and for cesarean section if indicated, should be immediately available. Adherent placenta, hemorrhage from faulty involution and other irregularities may characterize the third stage and early puerperium.

548 Medical Arts Building.

ABSTRACT OF DISCUSSION

DR. NORMAN F. MILLER, Ann Arbor, Mich.: Dr. Schauffler is to be commended for bringing this subject before us. The malformation is not a common one, but it occurs with sufficient frequency to merit attention, especially when one realizes that many of these patients come with a history of mismanagement due usually to misunderstanding. Some years ago I reported 54 cases of true uterus didelphys collected from the literature and 1 from our own clinic. There are three times in life when the presence of this malformation is likely to be noted. First, at adolescence, when some menstrual disturbance brings the patient for examination and the anomaly is discovered. Second, at the time of marriage, either because of dyspareunia or some other marital difficulty or in the course of a premarital examination. Third, it may be discovered by the physician during pregnancy, at the time of antepartum examination or during labor. While Dr. Schauffler's cases are mostly examples of uterus didelphys, case 7 appears to be better classified as an ordinary double uterus. In reporting these cases it would seem wiser to adhere to one type of malformation, as the type makes a difference in evaluating the incidence of complications. Generally the more extensive the malformation the higher the incidence of complication. In my experience labor was complicated, first, through interference with the presenting part; second, because of faulty power, and, third, by retention complications. Hemorrhage was not common. I subscribe to Dr. Schauffler's conservative attitude regarding the management of these cases. Sixty per cent of patients with this complication who become pregnant are likely to go to term, and 30 per cent of those who go to term have complications of some sort, the complication frequently being a minor one. Pregnancy need not be restricted in these patients. Fertility is usually not impaired and, as has been pointed out, the complications that do occur can be adequately taken care of provided the lesion is recognized. One must keep in mind that pregnancy may occur in both uterine horns. When this happens we probably have an indication for double cesarean section. Any anomaly of the lower generative tract should suggest the possibility of some malformation higher up.

DR. GOODRICH C. SCHAUFFLER, Portland, Ore.: Perhaps a psychologic factor is responsible for many of these misdiagnoses; the fact that we do not keep the condition in mind is responsible for many misdiagnoses. If we have any value in this presentation, it is perhaps a reemphasis of the simple and more available diagnostic measures. I refer specifically to the use of sounds and careful vaginal and cervical examination technic. Perhaps some of you have had the unfortunate experience of curetting a patient for therapeutic termination of pregnancy and having the patient go serenely on without terminating. We have all seen such cases and I believe that not infrequently it is the result of the invasion of an unsuspected nonpregnant horn of a double uterus. Also I believe occasionally a pregnancy in both horns may be responsible for such a condition; in fact, it has been reported more than once. Also in an elderly woman the invasion of such a double uterus for the diagnosis of cancer may give false results, owing to the revision of the wrong uterus by the cure.

SULFATHIAZOLE FOR ACUTE DIARRHEA AND DYSENTERY OF INFANTS AND CHILDREN

MERLIN L. COOPER, M.D.
RALPH L. ZUCKER, M.D.
AND
STEWART WAGONER, M.D.

STATISTICAL ANALYSES BY MRS. ESTELLE W. BROWN AND RUTH BENNETT, M.D.

CINCINNATI

Previous studies on mice by one of us (M. L. C.)[1] showed that one dose of 2 mg. of sulfathiazole or sulfapyridine administered by stomach tube three hours after the animals were infected with Shigella paradysenteriae (dysentery bacilli) resulted in survival of all mice inoculated with two minimum fatal doses, survival of the majority of mice inoculated with 100 minimum fatal doses and survival of a few mice inoculated with 1,000 minimum fatal doses.

Sulfathiazole was employed because our experience with the sulfonamide drugs indicated that sulfathiazole was tolerated better than sulfapyridine and also because our earlier experiments on mice showed that sulfathiazole and sulfapyridine were equally effective therapeutically. This study was started before sulfaguanidine became available, and the use of sulfathiazole was continued until a sufficient number of observations had been obtained from which conclusions could be drawn.

All patients were classified on admission into certain age groups: from birth to 6 months, from 6 months to 1 year, from 1 to 2 years, from 2 to 4 years, and over 4 years. Every other patient in each age group was treated with sulfathiazole.[2] The dose was 2 grains per pound (0.13 Gm. per 454 Gm.) of body weight a day administered by mouth. One half of the dose calculated for the first twenty-four hours was given as the initial dose. Subsequent doses were administered every four hours and each consisted of one sixth of the calculated dose for twenty-four hours. Administration of the drug was continued for three days after the patient's temperature became normal.

Special history sheets were prepared and pertinent information was recorded on them daily. The treatment of these patients consisted of that customary in our hospitals. Frequent determinations were made of the carbon dioxide combining power of the blood serum, and, when indicated, sodium bicarbonate was admin-

From the Children's Hospital Research Foundation and the Department of Pediatrics of the University of Cincinnati College of Medicine.

1. Cooper, Merlin L., and Keller, Helen M.: J. Pediat. **18**: 458-468 (April) 1941.

2. Supplied by E. R. Squibb & Sons.

istered. Blood transfusions were given when they would appear to be helpful, and parenteral fluids were administered when dehydration existed. Two stools were obtained for culture, usually within eight hours after the patient was admitted to the hospital. All stools were cultured on at least two Petri dishes each of sodium desoxycholate citrate medium, MacConkey's medium and S-S (Difco) medium. Suspicious colonies were picked and identified culturally and at times serologically. The details of the culture studies will be reported separately.

In order to evaluate the drug therapy, four factors were chosen for comparison, a procedure which largely obviated the question of individual judgment. These factors were (1) the length of time from admission until the patient's temperature became normal, (2) the length of time from admission until the patient's temperature became less than 100 F. (rectal), (3) the length of time from admission until the stools became normal and (4) the length of time from admission until the patient had apparently completely recovered or all symptoms had disappeared.

AGE DISTRIBUTION OF PATIENTS

In table 1 it is seen that there was a total of 123 patients studied from the Cincinnati General Hospital and the Children's Hospital. Fifty-nine, or 47.9 per cent, had S. paradysenteriae in their stools, which was the approximate incidence found in our previous study.[3] The incidence of dysentery in the respective age groups in the present study (table 1) increased from 19.5 per cent in patients in the first six months of life to 91.6 per cent in the group over 4 years of age.

STATISTICAL ANALYSIS OF DRUG THERAPY

A statistical analysis of the 64 patients whose stools were negative for S. paradysenteriae is seen in table 2. The mean days for the four factors chosen for analysis are compared in the control and the treated group. It

TABLE 1.—*Age Distribution and Incidence of Dysentery*

Patients	By Culture: Positive	By Culture: Negative	By Age	Per Cent Positive by Age
First 6 months	9	37	46	19.5
Second 6 months	14	19	33	42.4
Second year	17	6	23	73.9
3 and 4 years	9	1	10	90.0
Over 4 years	11	1	12	91.6
Total	59	64	123	47.9

TABLE 2.—*Sixty-Four Patients Whose Stools Were Negative for Shigella Paradysenteriae*

Mean Days from	Control	Treated	Value of P*
Onset to admission	6.2	7.4	0.6
Admission to normal temperature	6.7	7.3	0.6-0.5
Admission to temperature less than 100 F.	4.7	5.4	0.7-0.6
Admission to normal stools	5.8	5.5	0.9-0.8
Admission to recovery	8.1	9.1	0.5

* If P is 0.05 or less, the difference between the two groups may be considered significant.

is seen first that there was no significant difference in the mean days from onset of infection to admission to the hospital in the control and treated groups. This demonstrates that, for this important variable, these two groups were satisfactory for study. It is observed, as regards the four factors, that the value of P in each instance was far too great to indicate a significant difference. These findings led to the conclusion that the treated group of patients whose stools did not contain S. paradysenteriae derived no appreciable benefit from the drug.

The data from the statistical analysis of the 59 patients whose stools contained S. paradysenteriae and who had clinical dysentery are seen in table 3. Again it is noted that there was no significant difference in the mean days from onset of illness to admission to the hospital in the control and the treated patients, indicating that this was a satisfactory group of patients for such a study. The comparison of the control and the treated group from the standpoint of the four factors chosen for analysis shows, in each instance, a decidedly significant difference in favor of the treated group as judged from the value of P. It is interesting that sulfathiazole was effective only in the treatment of patients whose stool cultures were positive for S. paradysenteriae.

TABLE 3.—*Fifty-Nine Patients Whose Stools Were Positive for Shigella Paradysenteriae*

Mean Days from	Control	Treated	Value of P*
Onset to admission	6.1	4.1	0.7-0.6
Admission to normal temperature	10.6	5.2	0.01-0.001
Admission to temperature less than 100 F.	7.8	3.5	0.02-0.01
Admission to normal stools	11.2	4.7	<0.001
Admission to recovery	12.7	7.0	0.01-0.001

* If P is 0.05 or less, the difference between the two groups may be considered significant.

TABLE 4.—*Total Group of One Hundred and Twenty-Three Patients*

Mean Days from	Control	Treated	Value of P*
Onset to admission	6.2	5.9	0.9-0.8
Admission to normal temperature	8.8	6.4	0.05-0.02
Admission to temperature less than 100 F.	6.3	4.5	0.1-0.05
Admission to normal stools	8.5	5.2	0.01-0.001
Admission to recovery	10.5	8.1	>0.05

* If P is 0.05 or less, the difference between the two groups may be considered significant.

In table 4 all 123 patients, those with and those without dysentery, are compared after being divided into control and treated groups. The value for P for each of the four factors is significant and in favor of the patients treated with sulfathiazole. These significant differences are not so well defined, however, as are those obtained when only the dysentery patients are considered (table 3). This lessened significance is accounted for by the inclusion into this group of the nondysentery patients who did not derive benefit from the sulfathiazole.

A statistical analysis of the duration of illness among the control and the treated patients is seen in table 5, in which the patients are compared on the basis of stool cultures being positive or negative for S. paradysenteriae. It is to be noted that both groups were satisfactory for such a study (as judged by the value of P for the duration of illness from onset to admission to the hospital). If the control patients are considered first, it is seen that the value of P for three of the four factors is significant and in favor of the patients whose stool cultures were negative. The value of P was 0.08 for the fourth factor (the length of time from admission to the time when the temperature became less than 100 F.); this figure, although slightly above the upper limit of significance (0.05), would be considered acceptable by many statisticians. The interesting point is that the

3. Cooper, Merlin L.; Furcolow, M. L.; Mitchell, A. Graeme, and Cullen, Glenn E.: J. Pediat. **15**: 172-182 (Aug.) 1939.

significant difference in duration of illness is in favor of the patients with negative stools, indicating that they were sick a shorter time than were those patients whose stool cultures were positive for S. paradysenteriae when neither group received sulfathiazole. When the patients

TABLE 5.—*Duration of Illness in the Control and Sulfathiazole Treated Patients with Positive and Negative Stool Cultures*

Mean Days	Control			Sulfathiazole		
	Positive	Negative	P*	Positive	Negative	P*
Onset to admission	6.1	6.2	0.90	4.0	7.4	0.23
Admission to normal temperature	10.5	6.7	0.04	5.1	7.3	0.12
Admission to temperature less than 100 F.	7.8	4.7	0.08	3.5	5.4	0.16
Admission to normal stools	11.2	5.8	0.005	4.7	5.5	0.47
Admission to recovery	12.7	8.1	0.012	7.0	9.1	0.17

* If P is 0.05 or less, the difference between the two groups may be considered significant.

who received sulfathiazole are considered, it is seen that there was no significant difference in duration of illness between those whose stool cultures were positive for S. paradysenteriae and those whose stool cultures were negative. This absence of any significant difference was due to the shortening of the period of illness among the patients with positive stool cultures as a result of treatment with sulfathiazole. This point of view, together with the information seen in table 3 in which the treated and the untreated patients with positive stools are compared, emphasizes the fact that the drug was effective only in the patients with positive stools.

The patients in this study were not so acutely ill as those reported in a previous study.[3] It was desirable to know whether the patients in the present study had been seen earlier in the course of their illness. A comparison of the mean days from onset to admission in these two groups (table 6) shows that there was no significant difference in the days of illness before admission to the hospital, indicating that the patients in the present study did not receive hospital care any earlier than the previous and more acutely ill group.

The fatality rate among the patients in this study was lower than that in any group previously studied. There were 6 deaths, and 5 of these were among patients whose stool cultures were negative. Only 1 of the patients who died received sulfathiazole, and he was given the drug late in the course of his illness. Five of the deaths occurred in children under 5 months of age and 4 of the 6 had been sick less than one week before admission to the hospital.

TABLE 6.—*Mean Days from Onset to Admission Among Patients in the Years 1940 and 1938*

Patients	1940	1938*	P
Negative stool cultures	6.8	8.3	0.22
Positive stool cultures	5.2	6.2	0.57

* Onset to first stool, which was usually the day of admission.

Symptoms of drug reactions were noted in 6 patients. Of these, 2 showed microscopic hematuria on the third and seventh days of therapy respectively, at which times drug administration was stopped. In 4 other patients cutaneous lesions similar to erythema nodosum developed, a type of drug reaction apparently peculiar to sulfathiazole. These lesions as well as the hematuria disappeared promptly when drug therapy was stopped.

A comparison of the condition of the patients during the period they were in the hospital is seen in table 7. More patients whose stool cultures were negative were classified as being in a "poor" and "serious" condition, while more of those whose stool cultures were positive were classified as in "good" and "fair" condition. More patients treated with sulfathiazole were classified as being in a "poor" and "serious" condition, while more of those who did not receive the drug were in a "good" and "fair" condition.

In this study we are not justified in drawing any conclusion regarding the influence of sulfathiazole therapy on the disappearance of S. paradysenteriae from the stools, since no organized effort was made to obtain repeated stool cultures at regular intervals. However, the data (table 8) show that there was an average of three and two-tenths stools examined per patient in the group which received sulfathiazole and four and three-tenths stools per patient in the group which did not receive sulfathiazole. Only 1 of 17 patients treated with sulfathiazole still had a positive stool culture when discharged from the hospital. In comparison, 17, or 50

TABLE 7.—*Condition of Patients While in the Hospital*

	Patients			
	Good	Fair	Poor	Serious
By disease				
Negative stool	6	16	36	6
Positive stool	10	32	15	2
By treatment				
Sulfathiazole	5	21	29	4
No sulfathiazole	11	27	22	4

TABLE 8.—*Influence of Sulfathiazole on the Disappearance of Shigella Paradysenteriae from the Stools*

	Sulfathiazole		No Sulfathiazole	
	Patients	Stools Cultured	Patients	Stools Cultured
Stools became negative	16	53	17	79
Stools did not become negative	1	2	17	69
Totals	17	55	34	148

per cent, of 34 patients who did not receive the drug still had positive stool cultures at the time they were discharged from the hospital.[4]

SUMMARY

The stools of 59, or 47.9 per cent, of 123 patients suffering from acute diarrhea were positive for S. paradysenteriae, Flexner and Sonne.

All patients were classified into age groups on admission to the hospital, and every other patient in each age group was treated with sulfathiazole.

Four factors were chosen for statistical analysis and evaluation of the drug therapy. These factors were (1) the length of time from admission to the hospital until the patient's temperature became normal, (2) the length of time from admission until the patient's temperature became less than 100 F. (rectal), (3) the length of time from admission until the stools became normal and (4) the length of time from admission until the patient had apparently completely recovered.

Statistical analysis showed that sulfathiazole was of therapeutic value in patients whose stools were positive for S. paradysenteriae but was without demonstrable

4. Since this material was submitted for publication a similar study has been instituted in which sulfaguanidine is being used, and the results will be published in the near future.

effect in the treatment of patients whose stools were negative for S. paradysenteriae.

Six patients died. Five of these had negative stool cultures. Only 1 of these 6 patients received sulfathiazole, and in this instance the drug was started late. Four of the patients who died had been sick less than a week when admitted to the hospital.

Our data indicate that sulfathiazole hastens the disappearance of S. paradysenteriae from the stools of the treated patients.

Seventeen of 34 patients who did not receive sulfathiazole had positive stool cultures when discharged from the hospital, while only 1 of 17 patients treated with sulfathiazole had a positive stool culture at the time of discharge.

Elland Avenue and Bethesda.

ALCOHOL AND THE PEDESTRIAN IN TRAFFIC ACCIDENTS

THOMAS A. GONZALES, M.D.
AND
ALEXANDER O. GETTLER, PH.D.
NEW YORK

From time to time, publications have appeared on the effect of alcohol on the driving efficiency of operators of motor vehicles. Attempts have been made to correlate the amount of alcohol in the blood, urine or expired air of drivers in traffic accidents and to determine the lowest quantity of the intoxicant in blood, urine and expired air above which it would be reasonably safe to infer that an impairment of reactions and reflexes would occur. Among the observers who have studied this problem are Schwarz,[1] Heise,[2] Carlson,[3] Naville and Rosselet,[4] Turner [5] and Selesnick.[6] The Committee on Tests for Intoxication of the National Safety Council [7] has recommended that "all persons having a level of alcohol in the blood above 0.15 per cent by weight are sufficiently impaired to be unsafe drivers."

With the exception of work by Gerber,[8] who found a blood alcohol concentration above 0.15 per cent in 37.3 per cent of 314 pedestrians who were killed in traffic accidents, and our published studies,[9] we have been unable to find any reference in the literature on the relation of alcohol to fatal and nonfatal accidents involving pedestrians.

In an attempt to add to the meager data on this phase of the subject and to obtain information on the relation of alcohol to violent deaths other than traffic fatalities, a large number of quantitative alcohol determinations on all types of violent deaths were carried out as a routine measure for a number of years. Tables 2 and 3 represent that part of the study which is concerned with fatal traffic accidents.

In a study of 6,000 fatal accidents, some related and others unrelated to trauma, Gettler and Tiber,[10] taking into consideration the clinical histories, attempted to classify the relation of the physiologic effects to the alcohol content of the brain (table 1).

It is evident from table 1 that the brain alcohol content of persons who have partaken of a beverage containing alcohol ranges from 0.005 and 0.6 per cent. Occasionally figures above 0.6 per cent have been observed. During the past twenty years only 1 case has been encountered in which the brain alcohol content has been as high as 0.9 per cent.

An analysis of the table indicates that practically no abnormal physiologic effects occur in persons having a brain alcohol content below 0.1 per cent (1 plus).

Persons with a brain alcohol content of above 0.1 per cent and up to 0.25 per cent (2 plus) exhibited definite physiologic disturbances, as indicated in the table. In a majority of this group unbalanced equilibrium, staggering gait or other signs commonly indicative of "drunkenness" were absent. In some of the cases in which these phenomena were observed, values between 0.2 per cent and 0.25 per cent were obtained.

According to our studies, persons having a brain alcohol content of 0.25 per cent or more showed definite evidences of intoxication. By the term "intoxication" is meant unstable equilibrium, disturbances of the various faculties and incoordination resulting in a staggering gait. That this is true was demonstrated by Gettler and Freireich,[11] whether the person is a habitué or an abstainer, male or female, young or old, robust or sickly, and is based on the amount of alcohol present in the brain and not on the quantity of alcohol consumed by the person nor on the amount of alcohol found in the gastrointestinal tract. It is common knowledge that one person may become "dead drunk" from a given quantity of whisky while another person from the same quantity may show little or no effect. It is exactly for this reason that we are not concerned with how much alcohol the person has consumed nor how much is present in the gastrointestinal tract but emphasize that the brain or liver must be used for analysis in fatal cases. It is a well known fact that tolerance to alcohol depends on the rapidity with which the substance is oxidized in the tissues. A habitué has ordinarily acquired this property of oxidation to a high degree. If the same quantity of alcohol is consumed by an abstainer and a habitué, the rapidity of the oxidation process in the habitué prevents its accumulation in the brain to a greater degree than in the abstainer. Therefore the abstainer may show signs of intoxication while the habitué will remain apparently sober. The analysis of the brain will bear out this contention, namely the abstainer showing a large amount (3 plus) and the habitué considerably less, or 1 plus. Should the habitué continue to take alcohol, manifestations of intoxication may develop and a chemical analysis may reveal, after death, a brain alcohol content of 3 plus or more.

ANALYTIC PROCEDURES

Organs Best Adapted for Determining Alcohol Intoxication.—It is evident at the outset that the alcoholic content of the stomach and intestine is of no value

From the chemical laboratories of the Chief Medical Examiner's Office of New York City.

1. Schwarz, Fritz: Some Experiences in the Quantitative Determination of Alcohol Content of the Blood, Schweiz. med. Wchnschr. **67:** 54 (Jan. 16) 1937; abstr., J. A. M. A. **108:** 767 (Feb. 27) 1937.
2. Heise, H. A.: Alcohol and Automobile Accidents, J. A. M. A. **103:** 739-741 (Sept. 8) 1934.
3. Carlson, A. J.: Criteria of Acute Alcohol Intoxication, Science **80:** 546 (Dec. 14) 1934.
4. Naville, F., and Rosselet, E.: Difficultés et erreurs dans le diagnostic de la cause des morts dites "naturelle," Rev. méd. de la Suisse Rom. **48:** 742-749 (Sept. 10) 1928.
5. Turner, R. G.: Blood Alcohol and Its Relation to Intoxication in Man, Proc. Soc. Exper. Biol. & Med. **32:** 1548-1552 (June) 1935.
6. Selesnick, Sydney: Alcoholic Intoxication, Its Diagnosis and Medicolegal Implications, J. A. M. A. **110:** 775-778 (March 12) 1938.
7. Committee on Tests for Intoxication, National Safety Council, Chicago, Chemical Tests for Intoxication, Oct. 12, 1938, p. 12.
8. Gerber, S. R., Coroner, County of Cuyahoga, Cleveland: Personal communication to the authors, June 18, 1941.
9. Gonzales, T. A.: Annual Reports for 1935, 1936 and 1937 of the Office of Chief Medical Examiner, New York City, in the Report of Committee on Tests for Intoxication, National Safety Council, Chicago, Oct. 12, 1938, p. 5.
10. Gettler, A. O., and Tiber, A.: Arch. Path. & Lab. Med. **3:** 218 (Feb.) 1927.
11. Gettler, A. O., and Freireich, A. W.: Am. J. Surg. **27:** 328 (Feb.) 1935.

as an index of intoxication, for the reason that alcohol has no effect on the person until absorbed into the circulation. The alcohol in the gastrointestinal tract is still outside of the body proper, and its presence merely indicates that alcohol had been consumed, but it can in no way be taken as an index of intoxication.

TABLE 1.—*Classification of Alcoholics*[10]

	Alcohol Content of Brain, per Cent	Physiologic Effect
Trace	0.005-0.02	No noticeable effect
+	0.02 -0.10	Somewhat stimulated, no other noticeable effect
++	0.10 -0.25	Decreased inhibitions, emotional instability, some incoordination, loss of sense of care, talkative or taciturn, aggressive or retiring, slowing of stimuli response and decreased reaction time
+++	0.25 -0.40	Unstable equilibrium, disturbed senses, slurred speech, staggering gait
++++	0.40 -0.60	Deeply intoxicated, pronounced difficulty in locomotion, alcoholic coma

In several thousand fatal accidents the liver, brain, lungs, kidneys, spleen, spinal fluid, blood and urine were analyzed for alcohol. When the premortem history was compared with the alcoholic content of the organs analyzed in each case, it was revealed that the brain and the spinal fluid gave the best and most consistent indication of the degree to which the alcohol had influenced the subject in question. This is to be expected, as the condition of intoxication is caused by the action of the alcohol on the brain centers.

In cases in which the brain is not available, the liver may be used. It must be remembered, however, that the alcohol content of the liver may be a little higher (during the first hour of the absorptive period) or somewhat lower (postabsorptive period) than that of the brain. The difference between the alcohol content of the brain and of the liver is rarely more than 0.05 per cent. Between the second, third and fourth hour after the last drink has been taken, the alcoholic content of the brain and of the liver are practically the same.

In living persons the spinal fluid or the blood is preferred as a test medium to that of urine or expired air.

TABLE 2.—*Fatal Vehicle Accidents (New York City Ten Year Period) Classified According to Alcoholic Content of the Brain or Liver*

	Total Number of Cases	Alcohol Content of Brain: Absent	Traces	+ 0.02 to 0.1%	++ 0.1 to 0.25%	+++ 0.25 to 0.40%	++++ 0.40 to 0.60%
Pedestrians....	2,472	1,637	74	111	208	397	45
Subway and "L" road trains (falls from station platforms and run over)	421	180	10	26	59	138	8
Drivers of passenger cars....	214	85	9	13	51	50	6
Chauffeurs of trucks.....	44	38	2	2	1	1	..
Operators of motorcycles...	36	29	1	2	1	3	..
Drivers of horse drawn vehicles.....	11	6	..	3	..	1	1
Passengers in motor vehicles	273	142	6	26	39	56	4
Totals.....	3,471	2,119	102	183	359	644	64

Children under 15 years of age and adults who survived twenty-four hours or more subsequent to the accident are not included in this table.

The Method in Detail.—The brain, as soon as it is removed from the skull, is put into a clean receptacle, tightly covered and placed in a refrigerator. When ice cold, 500 Gm. is weighed out, quickly ground up and placed in a 2 liter flask; to this 600 cc. of water, 5 cc. of a saturated solution of tartaric acid and 1 cc. of white liquid petrolatum are added. The mixture is now distilled with steam. A long, well cooled condenser should be used, and the distillation should be continued until exactly 800 cc. has been collected. The distillate is well mixed and used in the following procedures.

Qualitative Detection.—Ten cc. of the distillate is put into a test tube. A copper spiral (10 turns of 14 gage copper wire) is heated red hot and plunged into the liquid. This is repeated ten times, the contents of the test tube being kept cool by allowing cold water to run over the test tube during the entire procedure. The copper oxide formed on the surface of the spiral during the heating oxidizes the alcohol, if present, to acetaldehyde. Four cc. of the oxidized distillate (when cool) is placed into a small test tube, and 0.5 cc. of a colorless reduced fuchsin solution[12] is added. After it has been allowed to stand for fifteen minutes the development of a red color indicates that alcohol is present. If it remains colorless, no alcohol is present and the directions that follow are omitted.

TABLE 3.—*Percentage of Cases in Fatal Automobile Accidents in Each of the Four Stages of Intoxication*

	Total Number of Cases	+	++	+++	++++	Percentage Under the Influence of Alcohol
Pedestrians in fatal automobile accidents..	2,472	4.5%	8.4%	16.0%	1.8%	30.7
Pedestrians in fatal elevated or subway train accidents.....	421	6.2	14.0	32.8	1.9	54.9
Drivers of passenger cars.....	214	6.1	24.0	23.4	3.0	56.5
Chauffeurs of trucks	44	4.5	2.3	2.3	...	9.1
Operators of motorcycles.....	36	5.6	2.7	8.3	...	16.6
Drivers of horse drawn vehicles.....	11	27.3	...	9.1	9.1	45.5
Passengers in motor vehicles.....	273	9.5	14.3	20.5	1.4	45.7

Quantitative Determination.—Twenty Gm. of potassium bichromate and 40 cc. of concentrated sulfuric acid are placed in a 500 cc. Kjeldahl flask. Three hundred cc. of the distillate previously obtained is now added and the contents are well mixed. The flask is then connected to a long, well cooled condenser by means of a Hopkins distilling head and the distillation started. The heat must be so regulated that it will take from forty-five to fifty minutes to collect exactly 250 cc. of distillate. After being thoroughly mixed, 50 cc. of this distillate is titrated with 0.05 normal sodium hydroxide solution, phenolphthalein being used as an indicator. From this titration figure, the percentage of alcohol present may be calculated as follows:[10] (cc. of 0.05 normal alkali used — 1.32) × 0.007.

In the analysis of blood or spinal fluid, 10 cc. together with about 1 Gm. of paraffin is placed in a 100 cc. distillation flask which is then set up for steam distillation. The flask containing the blood or spinal fluid is not

12. Dissolve 0.5 Gm. of fuchsin (basic) in 200 cc. of distilled water; add an aqueous solution of sulfur dioxide, the quantity corresponding to 1 Gm. of sulfur dioxide gas; allow to stand until the solution assumes an amber color (this requires about one hour). If too much sulfur dioxide is added, the solution is valueless after two days. If properly prepared, the fuchsin solution keeps well for several weeks.

heated. The steam alone is used for the distillation. One hundred cc. of distillate is collected. To this 100 cc. of distillate, placed in a 200 cc. round bottom flask, are added 7.5 Gm. of potassium dichromate and 15 cc. of concentrated sulfuric acid. The flask is connected to a long, well cooled condenser by means of a Hopkins distilling head. The contents are well mixed. A medium sized (1½ inch) Bunsen flame is applied, so that the distillation is not too rapid. The distillation should be at a slow but constant rate. It should take about sixty minutes to collect the required 80 cc. of distillate. When exactly 80 cc. has been collected, the distillate is well mixed and aliquot portions are titrated with 0.05 normal sodium hydroxide for the acetic acid produced. A small part of this distillate should be tested for the sulfate ion in order to be sure that no sulfur trioxide has passed into the distillate. If this procedure is followed, there should be absolutely no danger of sulfur trioxide being distilled. From the amount of acetic acid found by titration, the amount of ethyl alcohol is calculated as follows: [13]

Per cent alcohol = (cc. of 0.05 normal alkali needed for entire 80 cc. of oxidized distillate — 0.42) × 0.027.

By means of the methods described, 3,471 highway fatalities of all types covering a period from Jan. 1, 1928 to Dec. 31, 1937 were investigated. All cases were analyzed for methyl (wood) alcohol and, if it was present, were not included in this report. During this decade 6,911 necropsies were performed in a total of 12,897 highway deaths. The patients on whom tests were not made, and hence were not included in this investigation, were children under 15 years of age, adults who survived twenty-four hours or more subsequent to the accident (when any alcohol which might have been present at the time of the accident would have become completely oxidized and eliminated), and persons on whom for various other reasons the tests were considered unnecessary. Table 2 presents a classification of the 3,471 fatal vehicular accidents, on a basis of their alcohol content.

It will be noted from table 2 that the largest number of persons involved in accidents and having alcohol in their systems fall within the 2 plus and 3 plus groups. It may be assumed that the reason for this is that persons in the 1 plus group are hardly affected, if at all, while in the 4 plus group intoxication is usually so profound that locomotion is practically lost; in fact the majority are in a condition of alcoholic coma.

Table 3 classifies the total number of fatal accidents according to the percentage of cases in each of the four stages of intoxication.

The total number of fatalities of drivers (258) to that of pedestrians (2,893) indicates a ratio of 1 to 11. It is obvious that the driver is much better protected than the pedestrian and therefore less liable to fatal injuries. The greater percentage of brain alcohol content in intoxicated drivers who have met with fatal accidents may be accounted for by the smaller number of total fatalities in the drivers.

CONCLUSIONS

In evaluating the public health and medicolegal implications of highway accidents, the relation of alcohol to pedestrian deaths should not be ignored. The greater number of pedestrian fatalities as compared with the driver deaths and the results recorded in table 3, which indicate that 30.7 per cent of the pedestrians were under the influence of alcohol and that 26.2 per cent had an alcohol content of 2 plus or more, emphasize the importance of this obseravtion. Negligence on the part of the intoxicated pedestrian is also an important factor. The decreased inhibitions, deficient sense of care, impaired reaction time and slow response to stimuli of the intoxicated pedestrian tend to create a disregard for safety and for the proper observance of traffic regulations.

While this investigation was conducted in a city the population of which represents only a small proportion of the total population in the country, the figures obtained should be fairly representative of conditions in other large communities and should stimulate similar investigations elsewhere. Furthermore, the results of the investigations would be valuable in conjunction with other public health educational efforts in the reduction of fatal and nonfatal traffic accidents.

125 Worth Street.

13. Gettler, A. O., and Freireich, A. W.: J. Biol. Chem. **92**: 199 (July) 1931.

THE PRODUCTION OF EXPERIMENTAL OSTEOMYELITIS

PRELIMINARY REPORT

LOUIS SCHEMAN, M.D.
MARTHA JANOTA, M.S.
AND
PHILIP LEWIN, M.D.
CHICAGO

We present herewith a preliminary report on our experimental production of a lesion simulating human osteomyelitis. We are able to keep the animals alive for an indefinite period.

For years attempts have been made to reproduce in animals lesions of bones resembling human osteomyelitis. These experimental efforts have taught us much about the pathogenesis of the disease. That osteomyelitis is an infectious disease was early recognized. Beginning with Rodet [1] in 1884, Staphylococcus aureus was used to produce experimental lesions in bone. Rodet, and others shortly after him, produced abscesses in bones by injecting the organisms intravenously. Some years later Lexer [2] studied osteomyelitis extensively from the anatomic and pathologic points of view. His description of the circulation in the long bones stands unaltered. He recognized early that osteomyelitis was a hematogenous infection. Lexer produced bone abscesses by the injection of small amounts of attenuated bacterial cultures intravenously and noted that only in this way could the animals be kept alive and subsequently contract pathologic changes in the bone. Larger doses and more virulent cultures invariably caused death early in young animals and suppurative arthritis in older animals. Lexer stated that it was impossible by intravenous injection of staphylococci to produce an acute progressive medullary phlegmon.

This work has been amply corroborated, and there have been many reports of attempts to produce osteomyelitis in experimental animals by this means or some

From the Departments of Orthopedic Surgery, Bacteriology, Pathology and Roentgenology of Michael Reese Hospital.

This work was made possible by two equal grants from the Merriel Abbott and Lilly Marks Funds for Crippled Children.

In addition to those mentioned elsewhere, we received encouragement, assistance and guidance from Drs. Ludvig Hektoen, Edwin W. Ryerson, Hollis Potter, C. Howard Hatcher, Robert A. Arens and especially Dallas B. Phemister.

1. Rodet, A.: Compt. rend. Acad. d. sc. **99**: 569, 1885.
2. Lexer, Erich: Experimental Production of Osteomyelitis Foci, Arch. f. klin. Chir. **48**: 181, 1894, **52**: 576, 1896; Experiments with Osteomyelitis, ibid. **53**: 2666, 1896, **57**: 879, 1898.

modifications of it. Haldeman,[3] Starr,[4] Thompson and Dubos[5] and many others have injected staphylococci and other organisms both intravenously and directly into the bone and have claimed that they produced osteomyelitic lesions.

We have studied these various reports carefully and have repeated much of the work ourselves. We feel, however, that in the bone lesions which we and others have produced by these technics there are many points of dissimilarity to osteomyelitis as we see it clinically in the human subject. One cannot produce by these means a destructive lesion which is progressive. Moreover the suppuration is largely confined rather sharply to the site of inoculation or to the point where bacteria localize. We have repeatedly injected cultures virulent for the rabbit into the tibia without producing any demonstrable lesion or, at most, a small localized abscess. On intravenous injection of these bacteria we find that most of the animals die within a few days and that, along with abscesses in the liver, kidneys or spleen, one finds an occasional bone abscess. We have never obtained consistent results as reported by Thompson and Dubos. We have carried out many experiments in an attempt to induce a certain degree of immunity and hypersensitivity to whole bacteria and their products and have in no way modified our results.

Fig. 1.—Osteomyelitis of three weeks' duration involving the entire right tibia. Rabbit given a subcutaneous infection with Staphylococcus aureus followed in one week by injection of sodium morrhuate and bacterial culture as noted in E, under experimental method.

Never does one find massive destruction of an entire shaft or extensive periosteal reaction, or any definite formation of sequestrum and involucrum. For the most part the animals rarely live longer than a week, and there is no opportunity for associated experimentation.

Certain definite facts have been established with regard to the pathogenesis of osteomyelitis. Hobo[6] has enlarged on experiments of Lexer and Koch and has shown that after the intravenous injection of bacteria the organisms tend to localize particularly in the metaphysis, the epiphysis and the subperiosteal vascular regions. Hobo mentions the paucity of phagocytic elements in the metaphysis and also the anatomic arrangement of the blood vessels in this region, which is conducive to the slowing of the stream, both factors lending themselves to propagation of the organisms and development of infection.

Wilensky[7] emphasizes the importance of vascular thrombosis in the pathogenesis of osteomyelitis. He calls attention to the resemblance between the roentgenogram of aseptic necrosis of a long bone and that seen in some forms of osteomyelitis when the main nutrient vessel is involved in a thrombotic process. Phemister[8] in discussing aseptic necrosis of bone calls attention to vascular occlusion as a possible element in the pathogenesis of osteomyelitis.

Fig. 2.—Appearance two weeks after injection of the right tibial metaphysis with 0.3 cc. of sodium morrhuate. Note changes due to aseptic necrosis.

Robertson[9] has reviewed the subject of osteomyelitis thoroughly and emphasizes that trauma is by no means a factor necessary to the production of inflammatory centers in bone but calls particular attention to the fact that epiphyses bear the brunt of injuring stresses in children, even to the point of separation, rather than the periarticular structures, as is the case in more mature bones. Trauma insufficient to cause epiphysial separation undoubtedly produces hemorrhage with injury to cells and the resulting *locus minoris resistentiae*. With a "seeding" infection elsewhere the combination of factors may well cause an osteomyelitis.

In describing the past efforts to produce experimental osteomyelitis, Wilensky summarizes the reasons for failure and calls attention particularly to the difficulty in preparing the local field properly for embolus-thrombus formation. It is with the latter factor that we concerned ourselves in an effort to produce a true experimental osteomyelitis.

EXPERIMENTAL METHOD

Young rabbits of 2 to 2¼ pounds (900 to 1,020 Gm.) were used as the experimental animals. By injecting between 0.3 and 0.4 cc. of 5 per cent sodium morrhuate directly into the metaphysis of the tibia with a 23 gage

3. Haldeman, Keene O.: Acute Osteomyelitis: Clinical and Experimental Study, Surg., Gynec. & Obst. **59**: 25-31 (July) 1934.

4. Starr, C. L.: Acute Hematogenous Osteomyelitis, Arch. Surg. **4**: 567-587 (May) 1922.

5. Thompson, R. H. S., and Dubos, R. J.: Production of Experimental Osteomyelitis in Rabbits by Intravenous Injection of Staphylococcus Aureus, J. Exper. Med. **68**: 191, 1938.

6. Hobo, Teruo: Zur Pathogenese der akuten haematogenen Osteomyelitis, Acta scholae med. univ. imp. in Kioto **4**: 1 (March) 1921.

7. Wilensky, A. O.: Osteomyelitis: Its Pathogenesis, Symptomatology and Treatment, New York, Macmillan Company, 1934; Correlation of Roentgenographic Evidence with Clinical and Pathological Facts in Acute Osteomyelitis, Am. J. Roentgenol. **16**: 123-133 (Aug.) 1926; Mechanism of Bacterial Infection, Arch. Surg. **13**: 228-261 (Aug.) 1926; Pathogenesis of End Results of Lesions of Acute Osteomyelitis, Ann. Surg. **84**: 651-662 (Nov.) 1926; Mechanism and Pathogenesis of Acute Osteomyelitis, Am. J. Surg. **3**: 281-289 (Sept.) 1927.

8. Phemister, D. B.: Changes in Bones and Joints Resulting from Interruption of Circulation, Arch. Surg. **41**: 436-472 (Aug.) 1940.

9. Robertson, D. E.: Acute Hematogenous Osteomyelitis, J. Bone & Joint Surg. **9**: 8-23, 1927.

needle we hoped to produce sufficient vascular impairment in the bone to permit the growth of bacteria and the production of a lesion in bone. The animals were divided into the following groups:

A. Controls, which received from 0.3 to 0.4 cc. of sodium morrhuate alone into the tibial metaphysis.

B. Controls to determine whether the culture used in groups C to E would produce an osteomyelitis following injection into the bone or intravenously without preparing the bone field. This group does not include the many rabbits similarly injected prior to the experiments herein reported and referred to in our introductory remarks. The upper tibias of 3 rabbits were injected with 0.2 cc. of a 1 : 50 dilution of a twenty-four hour broth culture of Staph. aureus. Two rabbits received an injection of 0.2 cc. of a 1 : 100 dilution of a twenty-four hour broth culture of Staph. aureus intravenously.

C. Animals which received between 0.3 and 0.4 cc. of sodium morrhuate into the tibial metaphysis and one hour later 0.2 cc. of a 1 : 50 dilution of an eighteen to twenty-four hour broth culture of Staph. aureus into the same metaphysis. Of this group six animals received sodium morrhuate in both legs but culture only into the right tibia. The remainder received morrhuate and culture into the right tibia alone.

D. Animals which received from 0.3 to 0.4 cc. of sodium morrhuate directly into one tibial metaphysis

Fig. 3.—Section of region of tibial metaphysis (× 52) three weeks after injection of sodium morrhuate and Staphylococcus aureus as noted in C under experimental method. Note bone necrosis and purulent exudate.

and 0.2 cc. of a 1 : 100 dilution of an eighteen to twenty-four hour broth culture of Staph. aureus intravenously.

E. A group of animals which received an initial subcutaneous infection and one week later 0.3 cc. of sodium morrhuate into one tibial metaphysis followed in one hour by 0.2 cc. of a 1 : 50 dilution of a twenty-four hour broth culture of Staph. aureus into the same metaphysis. This group was a subsequent development in an attempt to produce some degree of immunity, enabling us to keep the animals alive for a longer period. The broth culture used was one which was originally obtained from a patient with hematogenous osteomyelitis and subsequently was passed through many rabbits.

The animals were observed from day to day for palpable swelling and were roentgenographed at weekly intervals. Involved bones were saved for microscopic

Fig. 4.—Region of osteoid columns of tibial metaphysis (× 100) four days after injection of sodium morrhuate. Note paucity of cellular elements in and about the osteoid tissue and irregular appearance of columns.

section when the animals died or were killed. Heart blood cultures were made on death, and also cultures from the involved bone.

RESULTS

A. Seven young rabbits served as controls. One tibia of each animal was injected with sodium morrhuate. Of these, 2 died on the second and fourth days respectively. The remaining 5 lived from three to eight weeks. Of the latter group 3 showed no bony changes in roentgenograms taken at weekly intervals over a period of four weeks or more. Two showed rarefying changes, one of the metaphysis and one extending down the shaft, which were considered to be indicative of aseptic necrotic changes. The microscopic findings varied. For the most part necrobiotic changes could be noted in the subepiphysial osteoid columns and in the marrow spaces, the latter being characterized by diminution in the cellular elements along with varying amounts of fibrotic change. Changes in bone trabeculae varied from practically none to considerable necrosis of metaphysial and inner shaft trabeculae as evidenced by the lack of normal staining qualities and absence of cells from lacunar spaces. Actual vascular thrombosis was not a significant feature. Reparative changes were well advanced in three weeks.

B. Of 3 control animals that received a culture injection into one tibia, 1 died the day following inoculation. The remaining 2 died in nine and seventeen days respectively. Neither of these animals developed a suppurative lesion involving the metaphysial bone. The 2 rabbits which received intravenous inoculation lived for twenty-two and twenty days respectively. At necropsy no bone infections were found. Both had abscesses in

the liver and kidneys, and Staph. aureus was recovered from the postmortem heart blood cultures.

C. This group, which received a preparatory injection of sodium morrhuate into the tibial metaphysis followed by an injection of staphylococcus culture consisted of 10 animals, 2 of which died the day following injection and 3 on the seventh, eighth and ninth days respectively. The remaining 5 lived between eleven and twenty-four days. Of the latter group 3 lived for approximately three weeks. All animals who lived longer than a week acquired lesions in the injected bone, interpreted as acute osteomyelitis. These lesions varied from multiple small abscesses with necrosis of trabeculae to massive necrosis of the entire shaft with formation of sequestrums and involucrums.

In some the infection involved the epiphysis with destruction of the epiphysial plate. Soft tissue abscesses were prominent and in nearly all there were large

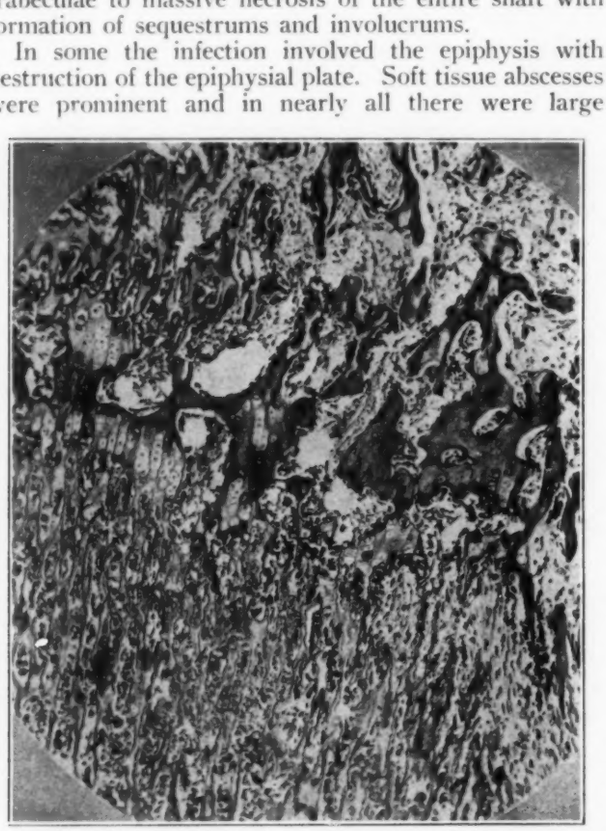


Fig. 5.—Zone comparable to that in figure 4 (× 52) twenty-four days after injection of sodium morrhuate. Note increased cellularity and appearance of active regeneration.

abscesses grossly, adjacent to the bone. The extent of the involvement depended apparently on the length of life of the animal. In 6 animals in which sodium morrhuate alone was also injected into the opposite tibia, clumps of bacteria were found in the metaphysis along with multiple abscesses. In 2 of the animals the degree of osteomyelitic involvement in the tibia which did not receive an original culture injection was more severe than that of the 1 that did. Staph. aureus was recovered from heart blood of all of the animals that died, and the same organism from the infected tibia.

D. Seven animals received Staph. aureus intravenously following the morrhuate injection into one tibial metaphysis. One animal died in two days and 2 in six and seven days respectively. Of the remaining animals 3 lived for approximately three weeks and 1 for twelve days. Of the animals that lived beyond a week, all acquired definite osteomyelitic lesions. In each case these lesions were characterized by extensive suppuration and sequestration. In 1 animal a secondary osteomyelitis was present in the lower femur of the opposite leg. This developed during the third week of infection. Microscopically the lesions were characterized by extensive bony necrosis with numerous abscesses and considerable periosteal new bone formation. The lesions progressed from week to week. Of this group 2 of the animals were killed on the twenty-fourth day and might have been observed over a longer period. Staph. aureus was recovered from heart blood culture of all the animals that died and from the involved bone.

E. This group, which received a preliminary subcutaneous infection a week prior to inoculation of the tibia with sodium morrhuate and culture, consisted of 15 animals. Four of the animals died immediately after receiving the injection of sodium morrhuate into the bone. These were the only deaths attributable to the injection of this substance. Of the remaining animals 2 lived for three weeks, 2 for two weeks and 1 for nine days; of the remaining 6, 5 were killed at the end of three weeks and 1 at the end of seven weeks.

Every animal in this group, except the 4 which died following the sodium morrhuate injection, contracted acute osteomyelitis of varying degree. In each case there was extensive suppuration in the bone and soft tissues, in some instances involving the entire shaft with sequestration a prominent feature. There was considerable periosteal new bone formation, frequent occurrence of subperiosteal abscesses and often destruction of epiphysis and epiphysial plate. In several instances the adjacent fibula was involved in a definite osteomyelitic process.

COMMENT

It would seem that some degree of immunity is imparted to the rabbits used in group E which permits survival over a period of time necessary for the development of an extensive osteomyelitis. Roentgen evidence of bone necrosis is evident at the end of the first week following infection and thereafter is progressive with the formation of sequestrums and involucrums in two and a half to three weeks. Many of the roentgenograms of the morrhuate control animals show no evidence of bone inflammation or destruction at any time. However, it is evident from the microscopic sections that this substance when injected into bone produces aseptic necrosis of varying degree. Its action appears to be directly on the marrow elements and bone trabeculae rather than by vascular occlusion. We have noted little evidence of the latter. The rapidity of bone repair following sodium morrhuate injection is startling, being well advanced at the end of three weeks, and it is difficult to find evidence of necrosis in some sections.

Whatever its mechanism, sodium morrhuate produces a certain amount of aseptic necrosis of bone, and this is apparently the soil necessary for the inception of and propagation of an infection the end result of which is osteomyelitis. The roentgen and microscopic picture of bone injected with sodium morrhuate alone is that of aseptic necrosis of mild degree, while that with sodium morrhuate followed by bacterial inoculation is one of severe bone destruction and suppuration.

From the invariable occurrence of osteomyelitis in group E it can be seen that, subsequent to the preparation of the bone field with sodium morrhuate, bacteria which are implanted directly or reach it by the hematogenous route are enabled to grow and produce extensive destruction of bone which on roentgenograms and microscopic sections resembles closely the disease as encountered in the human being.

The circulation in bone being of the end artery type, it may well be that, in human osteomyelitis, thrombosis or embolism prepares the field for bacterial growth by producing necrosis of bone. Once started, the process extends itself by further thrombosis, necrosis and infection.

SUMMARY AND CONCLUSIONS

Following the injection of sodium morrhuate into the tibial metaphysis of rabbits, a tibial osteomyelitis develops subsequent to the intravenous or local introduction of Staphylococcus aureus. Slightly more than 70 per cent of the animals that receive an immunizing subcutaneous infection live for three weeks or more. Those of the latter group which were killed at the end of three weeks might have lived longer.

Rabbits treated in this manner uniformly acquire osteomyelitis of a degree varying directly with the period of survival.

This, therefore, is a reliable method of producing experimental osteomyelitis in rabbits, which will permit experimentation subsequent to its development.

55 East Washington Street.

THE TREATMENT OF MYASTHENIA GRAVIS BY REMOVAL OF THE THYMUS GLAND

PRELIMINARY REPORT

ALFRED BLALOCK, M.D.
A. McGEHEE HARVEY, M.D.
FRANK R. FORD, M.D.
AND
JOSEPH L. LILIENTHAL JR., M.D.
BALTIMORE

Many observers have commented on the frequency of abnormalities of the thymus in patients with myasthenia gravis. Approximately one half of the reports of autopsies on patients with myasthenia gravis have contained descriptions of benign tumors, hyperplasia or persistence of the thymus. It is true, of course, that the autopsies on patients with myasthenia gravis are more apt to be reported if there is present some abnormality such as a tumor of the thymic region. On the other hand, it is likely that many small tumors or other abnormalities of the thymus have been overlooked at necropsy in a number of patients with myasthenia gravis. Norris [1] expressed the opinion that pathologic changes may be found in the thymus in cases of myasthenia gravis in direct ratio to the care with which they are sought.

The literature contains the descriptions of only a few attempts to influence the course of myasthenia gravis by surgical intervention. The first of these was a report by Schumacher and Roth [2] of an operation performed by Sauerbruch in 1912: A woman aged 21 had hyperthyroidism and myasthenia gravis. The important observations included the usual signs of hyperthyroidism and roentgenologic evidence of a mass in the anterior mediastinum. Three operations were performed. The first consisted of the ligation of the right superior thyroid artery and vein. An enlarged thymus was removed through an incision in the neck at the second operation. A subtotal thyroidectomy was performed eighteen months later. The patient improved but was not cured of the myasthenia at the time of the report by Shumacher and Roth. Haberer [3] included in his descriptions of operations on the thymus for other conditions a report of a partial thymectomy on a patient with myasthenia gravis. The operation was performed through an incision in the neck, and the thymus was described as being in a state of involution. When examined three years later, the patient appeared to be improved. The third and fourth patients were operated on by Sauerbruch and these operations were reported by Adler [4] and by Obiditsch.[5] In one of these, a benign thymic tumor the size of a child's head was removed and the patient died eight days later of mediastinitis. A tumor the size of a man's fist was removed from the other patient, who died five days later as a result of a streptococcic infection. Lièvre [6] stated in 1936 that there existed no report of the successful removal of a thymoma.

The fifth instance of an attempt to influence the course of myasthenia by an operation on the thymus was reported by Blalock, Mason, Morgan and Riven [7] in 1939, the operation having been performed three years previously. A cystic tumor was removed from the thymic region. No other thymic tissue was visualized, but the search of the anterior mediastinum was not a thorough one. This patient showed an early improvement and has been entirely well for four years. Campbell [8] has recently removed thymomas from 2 patients with myasthenia gravis. One of them died suddenly two days after the operation. The second patient is improved but myasthenia gravis still persists, as is proved by the fact that a prostigmine preparation is required. The remaining report is that by Leriche and Jung [9] of the removal of thymic tissue from a girl aged 16 years with myasthenia gravis. The incision was made in the neck well above the sternum. No improvement in the patient's condition was found two months after the operation.

The present attempt to influence the course of myasthenia gravis differs from those described in that the operation was performed with the deliberate purpose of removing all the thymic tissue by complete exploration of the mediastinum. The stimulus to try this procedure was based on several known facts. The abnormal physiology and pharmacology of this disease presents a picture similar to that of curare poisoning. It seemed reasonable to assume, then, that some particular tissue might be producing a substance similar in action to that of curare. That the thymus gland might be concerned in the production of such a substance was strongly suggested by the fact that the successful removal of a thymus tumor had been followed by a sustained remission of the disease in at least 1 instance. In addition, in a large majority of the cases carefully studied at autopsy some abnormality of the thymus has been found. As there is no other pathologic change

From the Departments of Surgery and Medicine of Johns Hopkins University School of Medicine and the Johns Hopkins Hospital.

1. Norris, E. H.: The Thymoma and Thymic Hyperplasia in Myasthenia Gravis with Observations on the General Pathology, Am. J. Cancer **27**: 421 (July) 1936.

2. Schumacher and Roth: Thymektomie bei einem Fall von Morbus Basedowii mit Myasthenie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**: 746, 1912.

3. Haberer, H.: Zur klinischen Bedeutung der Thymusdrüse, Arch. f. klin. Chir. **109**: 193, 1917.

4. Adler, H.: Thymus und Myasthenie, Arch. f. klin. Chir. **189**: 529, 1937.

5. Obiditsch, R. A.: Beitrage zur Kenntnis der Thymusgeschwülste, im Besonderen derjenigen bei Myasthenie, Virchows Arch. f. path. Anat. **300**: 319, 1937.

6. Lièvre, J. A.: Peut-on tenter un traitement chirurgical de la myasthénie, Presse méd. **44**: 991 (June 10-17) 1936.

7. Blalock, Alfred; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Myasthenia Gravis and Tumors of the Thymic Region, Ann. Surg. **110**: 544 (Oct.) 1939.

8. Campbell, Eldridge H., Jr.: Personal communication to the authors, 1941.

9. Leriche, R., and Jung, A.: Thymectomie dans un cas de myasthénie, Mém. Acad. de chir. **65**: 334 (March 1) 1939.

which occurs with such constancy, it was decided that a complete removal of all thymus tissue offered the best chance of altering the course of the disease and that a definite evaluation of the relation of this organ to the neuromuscular block present in myasthenia gravis should be made.

As there now exist methods of objective determination of the degree of severity of the myasthenic state on a quantitative basis, there can be no doubt whether or not improvement has taken place. Three methods of study have been employed in estimating the effect of thymectomy on the course of the disease: 1. A careful study has been made of the degree of weakness on a given dosage of a prostigmine salt and the degree of disability without any medication has been ascertained. 2. All patients have been carefully tested by the intra-arterial injection of prostigmine methylsulfate. It has been shown that in normal persons the injection of a small dose of prostigmine methylsulfate (0.1 to 0.5 mg.) into the brachial artery results in a profound weakness of the hand muscles as well as the appearance of numerous fasciculations.[10] In 9 of 10 patients with myasthenia gravis using much larger doses (1.5 to 3 mg.), there was observed an increase in strength of the hand muscles and no fasciculations have been observed.[11] 3. Not only do quantitative studies of the state of neuromuscular conduction using the method described by Harvey and Masland [12] show the specific changes characteristic of the disease, but these changes are proportional to the severity of the disease and leave no doubt as to the degree of alteration which any therapeutic procedure produces. This block in neuromuscular transmission is restored to or toward normal by prostigmine and returns to its abnormal state as soon as the drug is withheld. In 1 case studied during a spontaneous remission this characteristic defect in neuromuscular conduction did not even disappear.[13]

A brief description follows of the history and physical observations, the operation and the preoperative and postoperative course of the 6 patients on whom thymectomy has been performed. There was no evidence on roentgen studies of a mediastinal tumor in any of the patients.

REPORT OF CASES

CASE 1.—P. C., a Negro aged 33, noticed the sudden onset of diplopia and weakness of his legs eight months before admission. One month later, after an infection of the upper respiratory tract, the weakness became generalized and increased to such an extent that he had been confined to bed when he entered the hospital. He could not lift his head from the pillow, roll over in bed, hold even the lightest object in his hand or lift his leg off the bed. Improvement was dramatic after prostigmine bromide, but a total daily oral dose of 240 mg. was required before he could get out of bed and feed himself. Roentgenograms showed no evidence of thymic enlargement. Three mg. of prostigmine methylsulfate injected into the right brachial artery caused great improvement in strength immediately, but no fasciculations were seen.

On July 26, 1941 a thymectomy was performed after the sternum had been divided. There was a fairly large tongue of thymic tissue which extended from the suprasternal region to approximately the fifth costal cartilage. (Unfortunately we are unable to remember whether there were one or two lobes. In the remaining 5 cases there were two lobes.) There were no postoperative complications. Twenty-four hours later fasciculations were noticed in the tongue and arm muscles. He was given large doses of prostigmine for several days after the operation; the dose was gradually reduced, and he last received the drug on August 8.

The dosage of prostigmine bromide which he took prior to operation without any ill effects caused violent abdominal cramps and diarrhea when given several weeks following the operation. On August 30 1 mg. of prostigmine methylsulfate was injected into the brachial artery. There was still some gain in strength, but numerous fasciculations were visible and none had resulted from 2 and 3 mg. doses prior to operation.

The patient was discharged from the hospital on September 20. At the time of this report, which is two months after the operation, the patient is free of symptoms except for weakness of the hands, and no prostigmine has been given for seven weeks. His activity at present without drugs is greater than before operation when 240 mg. of prostigmine bromide a day was given. He no longer has diplopia or difficulty in swallowing. The legs have become quite strong and he is up and about all day.

CASE 2.—R. L., a white woman aged 28, a graduate student, with a typical picture of myasthenia gravis, had a sudden onset of diplopia and strabismus in August 1940. In October her legs grew weak and then her arm began to fatigue easily. A few weeks later she had difficulty with swallowing and her speech became nasal. In January 1941 the disease was diagnosed, and despite increasingly large doses of a prostigmine preparation her weakness grew progressively more severe. On admission she was taking, in addition to 1 Gm. of guanidine, six or seven 30 mg. doses of prostigmine bromide each day and still had ptosis, diplopia and nasal speech and was confined to bed because of weakness of the extremities. She was forced to take one or two doses of prostigmine bromide during the night because of difficulty in breathing. Roentgenograms of the chest showed no mediastinal mass. Fasciculations were not seen following the injection of 1.5 mg. of prostigmine methylsulfate into the brachial artery, and there was a great increase in strength of the hand muscles.

On August 4 a total extirpation of the thymus was performed. There were two long tongues of thymic tissue which extended from approximately the suprasternal region to the fifth costal cartilages. For several days after the operation she required large doses of prostigmine. Eight days after operation, the prostigmine dosage was reduced to half. Two weeks after the operation she required only 30 mg. orally each twenty-four hours. Twenty-two days postoperatively 0.6 mg. of prostigmine methylsulfate was injected intra-arterially. There was only a slight increase in strength and six to eight fasciculations a minute were observed. Since the twenty-fifth postoperative day she has required no medication.

Electromyographic studies on September 15 revealed that the action potential of the abductor digiti quinti muscle in response to a maximal stimulus applied to the ulnar nerve had risen from a preoperative level of 3.5 millivolts (while prostigmine was being given) to 5.8 millivolts without prostigmine. The daily variation in normal subjects has never exceeded 5 per cent; in this patient the gain was 60 per cent.

Her condition at present, seven weeks after the operation, is much better than her maximum improvement with the prostigmine salts before the thymus was removed. She talks more clearly, swallows without difficulty, reads and feeds herself and is again able to walk without assistance after nearly ten months in bed. Her feeling of fatigue after exercise is now a natural one in contrast to that before operation. The diplopia even on extreme lateral gaze has disappeared. Her improvement has been phenomenal, and it is her impression that she is making a total recovery.

CASE 3.—L. K., a Negro woman aged 22, contracted a febrile illness in August 1935 after which she first noticed generalized weakness most pronounced in the extremities, ptosis, diplopia, nasal speech and increasing difficulty in chewing and swallow-

10. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: On the Effects of the Intra-Arterial Injection of Acetylcholine and Prostigmine in Normal Man, to be submitted for publication in the Bulletin of the Johns Hopkins Hospital.

11. Harvey, A. M., and Lilienthal, J. L., Jr.: Observations on the Nature of Myasthenia Gravis: The Intra-Arterial Injection of Acetylcholine, Prostigmine and Adrenalin, to be submitted for publication in the Bulletin of the Johns Hopkins Hospital.

12. Harvey, A. M., and Masland, R. L.: A Method for the Study of Neuromuscular Transmission in Human Subjects, Bull. Johns Hopkins Hosp. **68**: 81 (Jan.) 1941.

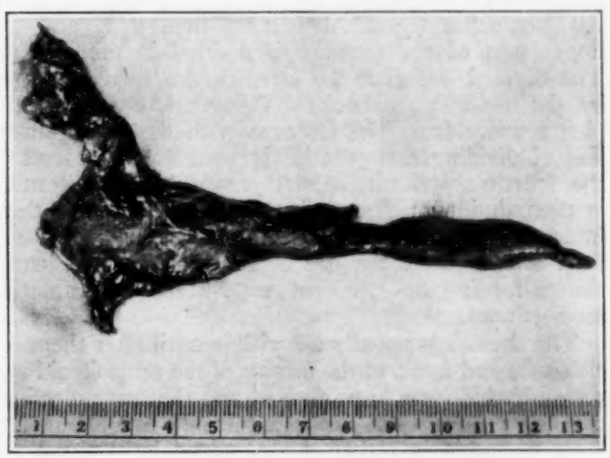
13. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: Observations on the Nature of Myasthenia Gravis: The Phenomena of Facilitation and Depression of Neuromuscular Transmission, to be submitted for publication in the Bulletin of the Johns Hopkins Hospital.

ing. She has had repeated infections of the upper respiratory tract, each of which resulted in an exacerbation of her symptoms. The symptoms were all improved by prostigmine. None of the other drugs used for the treatment of myasthenia gravis have afforded any relief, and during the last year, while she was taking 15 mg. of prostigmine bromide every two hours (105 to 120 mg. a day), her activities were nevertheless severely limited by weakness. Prior to operation, the intra-arterial injection of prostigmine methylsulfate produced a significant increase in local strength but no fasciculations. On Aug. 18, 1941, the thymus was removed (right lobe: 9 by 2.5 by 0.8 cm.; left lobe: 15 by 2.5 by 0.8 cm.). The left lobe is shown in the illustration. Her postoperative course was marked by a rise of temperature to 103 F. on the third postoperative day. On September 6 intra-arterial prostigmine methylsulfate produced a moderate increase in strength locally, and in addition there were numerous fasciculations in the injected arm. On September 18 she required only 15 mg. of prostigmine bromide four times a day and on this reduced dosage was definitely stronger than before the operation. By September 24 her daily dose of prostigmine bromide was only 30 mg. a day, given in four divided doses, and on this regimen her strength was increasing steadily.

CASE 4.—H. M., a white woman aged 39, noted the sudden onset in January 1936 of diplopia, difficulty in swallowing with regurgitation of liquids, and a nasal speech. There was never any subjective or objective evidence of weakness of the extremities. In September 1936 treatment with a prostigmine preparation was begun with decided improvement. A spontaneous remission occurred in July 1937 and continued until December 1938, at which time, following a severe infection of the upper respiratory tract, a return of her former symptoms occurred. From then on she required 15 mg. of prostigmine bromide six to eight times a day combined with 25 mg. of ephedrine twice a day. On this regimen she did well, but her constantly recurring infections of the upper respiratory tract produced periodic exacerbation of her symptoms which could not be controlled adequately with prostigmine. On admission Aug. 16, 1941 she was found to have typical myasthenic weakness of the muscles innervated by the cranial nerves, and, although there was no demonstrable weakness in the extremities, she did have slight dyspnea at rest. She complained of difficulty in breathing unless the head of the bed was elevated. Intra-arterial prostigmine methylsulfate produced moderate weakness in the injected area but improvement of the myasthenic symptoms elsewhere; and it produced five to six fasciculations a minute in the injected hand. The patient had a respiratory infection three weeks prior to her admission to the hospital, and codeine was required in order to control the cough at the time of her admission. Postponement of the operation was discussed but the patient said that she would probably not be free of a cold until the following spring.

Her thymus (right lobe: 9 by 3 by 0.8 cm.; left lobe: 15.2 by 2 by 0.5 cm.) was extirpated on August 21. The operation proceeded without untoward incident except that the intratracheal tube could not be introduced. This is the only patient who was not given intratracheal anesthesia. After the patient awakened, she refused to remain in the head depressed position. On the day following the operation she became restless, and rather large doses of morphine (16 mg. in four hour period) were required. The abdominal wall moved inward with inspiration. Bronchoscopic aspiration was considered but the patient died thirty-six hours after the operation before it was undertaken. Autopsy revealed atelectasis of the right and left lower lobes; the bronchi being filled with secretions. No remains of thymic tissue were found. In retrospect, several mistakes were made. The operation should have been postponed. The head-down position should have been insisted on, and the doses of morphine were too large. Bronchoscopic aspiration should have been performed when severe respiratory difficulty developed.

CASE 5.—R. S., a white housewife aged 30, first noted after the delivery of her second child in January 1941 the moderately rapid onset of generalized weakness. In April there appeared increasing bilateral ptosis and diplopia. In May there was rapidly progressive weakness of the extremities, and in June she first experienced difficulty in swallowing, associated with the development of nasal speech. During the months following her delivery she was amenorrheic and gained 35 pounds (15.9 Kg.). A search for the basis of this gain in weight has been unsuccessful and in the past month her menses have reappeared. She was studied here in July 1941 and found to have the typical myasthenic reaction to the intra-arterial injection of prostigmine methylsulfate and was discharged receiving prostigmine bromide 15 mg. three times a day and ephedrine three times a day, with only partial control of her myasthenic symptoms. Her thymus (right lobe: 8 by 2.5 by 0.8 cm.; left lobe: 8 by 2.5 by 0.8 cm.; left upper pole: 9 by 1 by 0.8 cm.) was removed on August 25. Her postoperative course was smooth. On September 15 the injection of prostigmine methylsulfate into the brachial artery produced moderate increased strength and in addition a few but definite fasciculations. Her requirement for prostigmine bromide, which had been 120 mg. a day preoperatively, had fallen to 60 mg. a day by September 18, and with this reduced dosage her diplopia and ptosis occurred only after prolonged reading; she had no difficulty with swallowing and she was able to walk about the ward without the fatigue which had been present before operation. Extraocular movements which were quite weak preoperatively are definitely improved. On September 24 the prostigmine bromide dosage was 52.5 mg. a day and a slow return of strength continues.



The left lobe of the thymus of patient 3. The right lobe was slightly smaller.

CASE 6.—M. W., a white housewife aged 34, experienced in July 1939 a relatively rapid onset of generalized weakness especially of the extremities, ptosis, diplopia, difficulty in speech and chewing and slight exertional dyspnea. She was treated in February 1940 with a prostigmine salt with definite improvement, and while receiving prostigmine bromide 15 mg. four times a day was able to be up and about despite moderate fluctuations in her strength. In June 1940 she was placed on a regimen of prostigmine bromide 15 mg. six times a day and ephedrine 25 mg. three times a day. She did well until the spring of 1941, when increasing weakness forced her to take prostigmine bromide 15 mg. every two hours both day and night. Despite this dosage she was unable to walk by herself and experienced difficulty in catching her breath even at rest. In August 1941, the injection of prostigmine methylsulfate into the brachial artery produced local return of power but no fasciculations. The thymus was removed on August 30. There were two lobes, each of which measured approximately 12 by 2.5 by 8 cm. A small opening was made in the left parietal pleura during the operation. On September 13 the intra-arterial injection of prostigmine methylsulfate produced a questionable degree of weakness in the injected arm and rare fasciculations. The postoperative course was distinguished by the fluctuations in the degree of strength and the prostigmine bromide requirement varied between 90 and 130 mg. a day. During the third week in September there was some slight improvement, but it is not pronounced as yet.

THE OPERATION

Thymectomy is a tedious but not a particularly difficult procedure. The main points in need of emphasis are that the thymus is situated almost exclusively in the thorax rather than in the neck and that it is impossible to remove it with any degree of certainty without exposing the anterior mediastinum through an adequate incision.

General anesthesia was produced by an induction with nitrous oxide and oxygen and the subsequent use of oxygen-ether. An intratracheal tube was inserted in all instances except 1. If care is used, one is not likely to make an opening in the pleura, but the tube allows one to aspirate frequently and thus to maintain the airways free of secretions and open. The respiratory movements during the operation are almost solely diaphragmatic or abdominal.

The incision is a longitudinal one, extending from just below the cricoid cartilage, down the midline of the sternum to the fourth costal cartilages. The sternohyoid muscles are separated in the midline. An index finger is then inserted under the manubrium of the sternum, maintaining close contact with the bone, and the right and left layers of pleura are pushed laterally. A Shumacher sternal divider is then used and the upper part of the sternum is divided in the midline. The divided edges of the sternum are then separated by the use of bone hooks. This plan of pushing the pleura away from the sternum with the index finger and of dividing this part is repeated until the level of the fourth costal cartilages is reached. The sternum is then divided transversely at the level of the third interspaces. The divided edges of the sternum are then separated by the use of self-retaining retractors, thus affording an excellent exposure of the anterior mediastinum.

The thymus is usually not visible until after the muscle tissue and fascia at the origins of the sternohyoid and sternothyroid have been divided and the two reflections of pleura have been separated in the midline. The layer of fascia is rather dense, particularly above the level of the left innominate vein, and it must be divided if the thymus is to be seen clearly. The greater part of the thymus lies below the level of the left innominate vein, and in most instances the tissue extends to the level of the fifth costal cartilages. There are usually two lateral lobes which are in close contact along the middle line, and they may be united. They usually extend rather far laterally beneath the pleura. The thymus is attached by tissue which is not very dense to the ascending aorta and the pericardium. There are a number of thymic arteries and veins, most of which appear to be branches of the thyroid or internal mammary vessels. In most instances, the two lobes of the thymus extend up to the inferior poles of the thyroid gland. The thymus is removed by sharp and blunt dissection, care being taken not to injure the pleura. The vessels are doubly ligated and divided. The most likely mistake is that one lobe of the thymus may escape detection. This may have occurred in case 1, but the progress of the patient does not support this possibility.

After the removal of both lobes of the thymus, the incision is closed without drainage. The divided edges of the sternum are approximated with two encircling sutures of braided silk. The soft tissues are approximated with several rows of interrupted sutures of silk.

A more detailed description of the operation together with illustrations will be published at a later date.

THE THYMUS

The operation revealed the presence of definite persistent thymic tissue in all patients. No gross tumors were visible. Thymic tissue was as easily differentiated from the surrounding structures as is the thyroid.

Most of the tissue which was removed was frozen immediately after the operation in order that it might be preserved for future studies. Multiple sections were made through the glands with a razor at a subsequent time, and no tumors were demonstrated. This was performed by Dr. Arnold Rich and the microscopic examination of the tissues will be reported in detail subsequently. Definite hyperplasia was present in all cases except 1. No adenomas were present. The sections from several of the patients revealed the presence of germinal centers.

PREOPERATIVE AND POSTOPERATIVE TREATMENT

The onset of symptoms of myasthenia gravis is frequently accompanied by an infection of the upper respiratory tract. A similar infection is most frequently the precipitating cause of an exacerbation and often results in death, as the beneficial action of prostigmine preparations under these conditions is greatly reduced. Even the mildest infection is dangerous, and for these reasons the most important point in the preoperative and postoperative care of these patients is the prevention of complications, since even those usually considered trivial may prove disastrous to the patient with myasthenia.

Operation should not be considered if there has been any history of an infection for the preceding ten to twelve weeks. This is not only to lessen the danger of an infection in connection with the surgical procedure but also to allow full recovery from the exacerbation of the disease which almost invariably accompanies such an infection.

The patient should enter the hospital several days before the operation to allow a period of rest with adequate doses of prostigmine. Mask isolation should be instituted during this period to prevent infections of the upper respiratory tract. Cross matching with an available donor should be carried out before the operation and enough sulfathiazole or sulfadiazine should be given to maintain a blood level of 5 to 6 mg. per hundred cubic centimeters.

Thirty minutes before the induction of anesthesia 1.5 to 2.5 mg. of prostigmine methylsulfate, 0.6 mg. of atropine sulfate and 10 mg. of morphine sulfate are given subcutaneously. Induction is effected with nitrous oxide and oxygen. A tube is then inserted into the trachea with great care and as little trauma as possible. Ether and oxygen are administered through a closed system. One of the most interesting observations has been the very small amount of ether required.

At the end of the operation (usually one and one-half to two hours after induction) 1 to 1.5 mg. of prostigmine methylsulfate and 0.6 mg. of atropine are given subcutaneously. Before the intratracheal tube is removed suction is applied. In order to lessen the chances of aspiration, the head is lowered by elevating the foot of the bed on 12 inch blocks for thirty-six to forty-eight hours after the operation. The patient is turned frequently. Respiratory difficulties may appear suddenly, so that the following apparatus are kept in readiness in the patient's room: a suction apparatus, an oxygen tent, a laryngoscope and a respirator. The patient has a special nurse who is instructed to make frequent observations of pulse and blood pressure and above all the character and frequency of the inspiratory

movements. An inward movement of the abdominal wall with inspiration is an early indication of difficulty. The postoperative complications to be anticipated are mainly respiratory—atelectasis and pneumonia. These patients withstand complications poorly and tire quickly with unusual respiratory effort. If treatment does not result in prompt relief, the immediate use of a respirator should be considered. It may be advisable to accustom the patient to the respirator preoperatively. The respirations even preoperatively may be mainly diaphragmatic.

Mask isolation is continued for six to eight days after the operation and sulfadiazine is administered until there has been no fever for two days. A portable roentgenogram of the chest is taken routinely each of the first two days following the operation. A widening of the mediastinal shadow has been observed in all patients in the early postoperative period.

Nothing is given by mouth until the day following operation. From 2 to 3 liters of physiologic solution of sodium chloride and 5 per cent dextrose are given intravenously in the first twenty-four hours.

The postoperative dosage of prostigmine is based on the amount received preoperatively. Usually 1 to 1.5 mg. of prostigmine methylsulfate subcutaneously is necessary every two hours for the first postoperative day. After this, 30 to 45 mg. of prostigmine bromide is given orally every two to three hours. There is usually an increased need for the drug during the first two days after thymectomy and not until two to three weeks later does the degree of improvement permit reduction well below the preoperative amounts. Prostigmine causes an increase in the bronchial secretion and saliva. In addition, spasm of the bronchial muscles induced by prostigmine may occur unless fairly frequent doses of atropine are given (0.4 to 0.6 mg. every four to eight hours seems to be a sufficient amount). When improvement takes place, symptoms indicating overdosage of prostigmine such as abdominal cramps appear and the dosage should be reduced.

Morphine has seemed best for the relief of pain postoperatively. The effective and toxic dose, however, is much reduced by the synergistic action [14] of the prostigmine salt and the maximum amount given should not exceed 8 mg. every four hours. The usual indication is pain at the site of operation.

Local anesthetics should not be used unless absolutely necessary [15] and then given only with an extra dose of the prostigmine salt. The amount of all anesthetic agents should be kept as small as possible. Most of the patients have required almost no anesthetic during the last hour of the operation, and yet they regained consciousness very slowly after the procedure was completed. This may have been due to the preoperative dose of morphine, whose effect was prolonged by the synergistic action of prostigmine, or to some fundamental alteration in the effect of anesthetic agents on individuals with this disease.

It is well to emphasize again the fact that these patients withstand complications poorly. Aronson [16] reported recently the death of a patient with myasthenia gravis which occurred twenty-four hours after irradiation of the thymic region. Dr. Viets of Boston informed us of the death of a patient which followed the introduction of a small quantity of air beneath the sternum. The procedure was carried out in an attempt to demonstrate a tumor of the thymus. Sudden and unexpected death is not rare in patients with myasthenia gravis.

14. Bernheim, F., and Bernheim, M. L. C.: Action of Drugs on the Choline Esterase of Brain, J. Pharmacol. & Exper. Therap. **57:** 427 (Aug.) 1936. Slaughter, D., and Gross, E. G.: Some New Aspects of Morphine Action: Effect on Intestines and Blood Pressure; Toxicity Studies, J. Pharmacol. & Exper. Therap. **68:** 96 (Jan.) 1940.

15. Harvey, A. M.: The Actions of Procaine on Neuromuscular Transmission, Bull. Johns Hopkins Hosp. **65:** 223 (Sept.) 1939.

16. Aronson, S. F.: Myasthenia Gravis: A Discussion, with Presentation of a Case Associated with a Thymoma, Ann. Int. Med. **15:** 137 (July) 1941.

SUMMARY

In this preliminary report of the effects of total thymectomy on the course of myasthenia gravis, the early results are encouraging and suggest strongly that the thymus gland is concerned in some manner in the genesis of myasthenia gravis. The observations suggest furthermore that the thymus is a gland with an internal secretion and that it may have a definite function.

ADDENDUM.—One month after this report was completed and submitted for publication, the course of the first three patients continued to be satisfactory. There is a progressive improvement of strength, and no prostigmine or other therapy is required. The improvement of patients 5 and 6 is less striking thus far than was anticipated in view of the previous experiences. It is possible that an abnormality of the thymus alone is not responsible for the disease and that the role of the thymus may vary in importance in different patients. Other factors, if any, which may be involved in the genesis of myasthenia gravis are matters of conjecture. The possibility remains that removal of the thymus simply breaks a chain of abnormal conditions and thus influences the course of the disease. On the other hand, the dramatic improvement of most of the patients indicates that the thymus is concerned directly in the pathogenesis of myasthenia gravis. Retardation in 1 patient may be due to the development of an acute infection of the respiratory tract.

Clinical Notes, Suggestions and New Instruments

FINAL REPORT ON THE IDENTIFICATION OF THE ORGANISM OF THE PREVIOUSLY REPORTED CASE OF SUBACUTE ENDOCARDITIS AND SYSTEMIC MYCOSIS (MONILIA)

S. H. POLAYES, M.D., BROOKLYN
Pathologist, Cumberland Hospital
AND
C. W. EMMONS, PH.D., BETHESDA, MD.
Senior Mycologist, National Institute of Health

In the report of the first case of subacute endocarditis with systematic moniliasis ever to have been clinically diagnosed and published [1] it was not possible to state the identity of the causative organism, although it was definitely known to be a species of Candida (Monilia). Since then, however, studies of cultures which had been submitted to the Division of Infectious Diseases of the U. S. Public Health Service have led to the definite identification of the fungus as Candida (Monilia) parakrusei. Because numerous requests have been made for the final results of our studies, it was deemed advisable to publish them at this time.

The following, therefore, is a brief summary of the mycologic studies of the organism, including some of the more pertinent features mentioned in the previous publication. The present report also affords us the opportunity to publish a reproduction of a photomicrograph of a typical smear from a colony of one of the original blood cultures obtained early in the course of the patient's illness. This illustration was inadvertently omitted from the original publication and would have been figure 8.

Growth on culture on Sabouraud's agar yielded budding ovoid bodies about 4 microns in diameter; hyphae were very rare; cornmeal agar yielded budding ovoid cells from 3 to 4 microns in diameter on the surface; hyphae below the agar

1. Joachim, Henry, and Polayes, S. H.: Subacute Endocarditis and Systemic Mycosis (Monilia), J. A. M. A. **115:** 205 (July 20) 1940.

surface were delicate, short and branching freely but producing few buds.

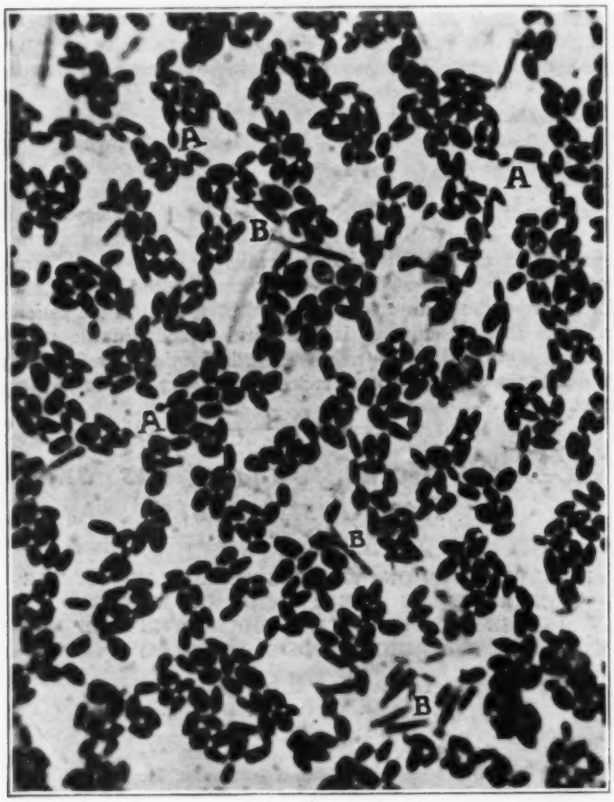
On staining, the yeasts were gram positive except for an occasional pink hypha.

Reproduction was by budding.

Growth characteristics were as follows: In acid dextrose broth after forty-eight hours at 37.5 C. there was growth settling to the bottom and clinging to the side of the tube; the broth was clear except in a few tubes. There was no ring or the ring was barely noticeable at an angle formed by the broth surface and the side of the tube.

On acid dextrose agar after ten days at 30 C. the colonies were ivory to yellow and glistening with margins smooth or slightly scalloped.

On blood agar after ten days at 37.5 C. culture yielded gray, smooth, glistening, nonhemolytic, low dome-shaped colonies with even borders from 2 to 3 mm. in diameter.



Gram stain of a typical smear of one of the colonies of Monilia obtained by blood culture. Note (*A*) budding and (*B*) elongated forms which suggest the description of atypical mycelia. Reduced from a photomicrograph with a magnification of 1,500 diameters.

Sugar reactions were as follows: There were acid and gas formations in dextrose and levulose broths but not in sucrose, lactose, maltose and raffinose. The amount of gas formation varied, only small bubbles appearing in most tests. (The fermentation reactions are those found on examination of cultures studied by the Division of Infectious Diseases of the U. S. Public Health Service. Studies of previous cultures made in the laboratories of the Cumberland and Bellevue hospitals showed approximately 10 per cent gas formation in maltose, saccharose and dextrose.)

CONCLUSIONS

There are slight discrepancies between the various published descriptions of C. parakrusei. Our strain has been somewhat variable in growth characteristics over the period of time it has been studied. The instability of these yeastlike fungi is well known and explains in part the discrepancies in descriptions and the difficulty of identifying some strains. This strain can, however, be definitely identified as C. (Monilia) parakrusei. We believe that it is closely related to Candida krusei.

North Portland Avenue and Auburn Place.

PARALDEHYDE POISONING

REPORT OF A FATALITY

MERVYN SHOOR, M.D., SAN FRANCISCO
Lieutenant (j. g.), Medical Corps, United States Navy

Death from paraldehyde poisoning is rare. Kotz [1] reviewed the literature up to 1938 and reported a case of his own in which death ensued following the use of 31 cc. of paraldehyde rectally in a patient with a toxemia of pregnancy.

Since it was introduced about sixty years ago by Cervello [2] and Strahan,[3] paraldehyde has been used extensively as a hypnotic and sedative in a variety of medical conditions and, more recently, has been found to be a useful adjunct in the field of obstetric analgesia.

According to the standard works on pharmacology and toxicology, paraldehyde is considered a safe hypnotic and sedative. Sollmann [4] states that its actions are similar to alcohol but that its hypnotic effects are more rapid and efficient. "Its acute toxicity is low, so that 100 Gm. produced only very prolonged sleep." He adds that "therapeutic doses do not tend to depress the heart or respiration." Webster [5] states that "the fatal dose of paraldehyde is difficult to state, as very large quantities have been taken without serious consequences other than prolonged unconsciousness." Gonzales [6] concurs in this respect, stating that "the fatal dose is uncertain." Leschke [7] states that recovery has occurred from as much as 150 Gm., and he recorded a case in which death occurred following administration of 52 Gm. of the drug.

An anonymous writer reported a case to the editor of the *Lancet* [8] in which death occurred after administration of 6 or 7 teaspoons of paraldehyde to a typhoid patient. Hanson [9] reported a case of poisoning, followed by recovery, which occurred after 120 cc. had been given by mistake to a woman in labor. Brown [10] reported another case after the ingestion of 16 cc. of the drug, but recovery ensued within twenty-four hours. The last case that has been reported is one by Jinkins [11] in which poisoning resulted after 24 cc. was given rectally to a woman in labor; after a stormy course there was a complete recovery.

The case reported here is unique in that only 12 cc. of paraldehyde rectally resulted in fatal poisoning. This is the smallest dose of the drug on record to cause death.

CLINICAL SUMMARY

Mrs. J. S., a primipara aged 21, was admitted to the private service of Mount Zion Hospital at 12:05 a. m. on July 3, 1940. Her past history had been singularly free of disease; she stated that she had not had even the usual childhood exanthematous diseases and that she had had no operation or previous hospital entry. She considered herself to have enjoyed excellent health always.

Her last menstrual period was Sept. 22, 1939 and the expected date of confinement was June 29, 1940. The antepartum course had been entirely free of complications. Pelvic measurements were within normal limits. During the ninth month of pregnancy she had noted slight edema of the ankles in the evenings.

Spontaneous rupture of the membranes occurred at 10:30 p. m. on July 2 and she entered the hospital shortly thereafter. At that time, she was not in labor. She was well developed and well nourished. Her weight was 196 pounds (89 Kg.), the temperature 37 C. (98.6 F.), pulse rate 80 and respiratory rate 18 a minute. The heart was normal in size; the sounds were regular and of good quality. There were no murmurs.

From the Obstetrical Service, Mount Zion Hospital.

1. Kotz, Jacob; Roth, G. B., and Ryon, W. A.: Idiosyncrasy to Paraldehyde, J. A. M. A. **110**: 2145 (June 25) 1938.
2. Cervello, V.: Arch. ital. de biol. **6**: 113, 1884.
3. Strahan, S. A. K.: Lancet **1**: 201 (Jan. 31) 1885.
4. Sollmann, Torald: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 731.
5. Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1930, p. 751.
6. Gonzales, T. A., and others: Legal Medicine and Toxicology, New York, D. Appleton-Century Company, Inc., 1937, p. 532.
7. Leschke, Erich: Clinical Toxicology, translated by C. P. Stewart, Baltimore, William Wood & Company, 1934, p. 185.
8. Lancet **2**: 243, 1890.
9. Hanson, Samuel: California & West. Med. **47**: 191 (Sept.) 1937.
10. Brown, Gilbert: Brit. J. Anesth. **13**: 25 (Oct.) 1935.
11. Jinkins, J. L., and Herrod, J.: Bull. John Sealy Hosp. & Univ. Texas School of Med. **1**: 27 (Feb.) 1939.

The lungs were free of abnormalities by percussion and auscultation. The blood pressure was 130 systolic and 90 diastolic. Examination revealed that the baby was in the right occipitoposterior position, that the head was floating and that there was no cervical dilatation. Urinalysis revealed albuminuria (++ degree), and from 8 to 10 red blood cells per high dry field microscopically. The hemoglobin was 9.2 Gm. per hundred cubic centimeters of blood; red blood cells numbered 3,480,000 and the white blood cells 7,350 with a normal distribution.

After a soapsuds enema contractions of moderate severity commenced at 12:30 a. m. on July 3. These continued rhythmically and the cervix slowly dilated. Because the patient was a Christian scientist she refused sedation, but on July 4 she acquiesced and, accordingly, at 9:30 a. m. 12 cc. of paraldehyde in 6 cc. of benzyl alcohol and 30 cc. of physiologic solution of sodium chloride were administered rectally. This she retained. At this time, the cervix was completely dilated, but the head remained in the right occipitoposterior position above the spines. Analgesia was excellent. The patient slept between contractions and became somewhat restless when they occurred. She was taken to the delivery room at 1 p. m. At that time, the anesthetist observed the pulse to be 148 a minute and irregular. The respirations were 48 a minute, deep and labored; the nail beds and ears were cyanotic. She did not seem to respond to the ordinary physical stimuli.

Low forceps (Tucker-MacLean) were applied under light ether anesthesia and a living baby girl weighing 9 pounds, 7 ounces (4,280 Gm.) was delivered from the right occipitoposterior position. A second degree midline episiotomy was performed and repaired. A proprietary uterine stimulant 1/320 grain (0.2 mg.) was administered intravenously. She was returned to her room at 2:30, still stuporous, with the pulse regular at 130; respirations remained rapid.

In order to rule out the possibility of diabetic coma, urinalysis was repeated. This showed strong reduction with Benedict's solution and a strongly positive acetone reaction, with a trace of diacetic acid. The blood sugar was 72 mg. per hundred cubic centimeters. One cc. of metrazol was administered intravenously and the patient was placed in an oxygen tent.

At midnight, the pulse was 144 and regular, the blood pressure was 96 systolic and 56 diastolic, and the respirations were 36, deep and stertorous. She responded slightly to painful stimuli and occasionally attempted to open her eyes, but otherwise she remained comatose. The pupils reacted to light. The deep tendon reflexes were absent, but there were no abnormal reflexes. A total of 20 cc. of nikethamide was given intravenously in divided doses over a period of five and one-half hours, without benefit. An intravenous infusion of dextrose was started. Despite these supportive measures pulmonary edema gradually ensued, and at 5:30 a. m. on July 5 a generalized convulsion occurred. Carpopedal spasm and a positive Chvostek sign were elicited. The patient died at 7 o'clock, some eighteen hours after delivery and about twenty-one and one-half hours after administration of the paraldehyde.

The baby on admission to the nursery weighed 9 pounds 7 ounces. She was cold to the touch and her breathing was shallow. She had repeated bouts of cyanosis followed by convulsions, and despite inhalations of carbon dioxide and oxygen she died thirty-one hours after delivery.

An autopsy on the body of the mother, which was performed by the coroner's office of San Francisco twelve hours after death, revealed the following conditions: "Acute pulmonary congestion and edema, subpleural and subpericardial hemorrhages consistent with asphyxia, pericarditis and adrenal apoplexy. Negative for poisons."[12] The toxicologist reported only traces of paraldehyde in the blood, urine and gastric contents. An autopsy was not done on the body of the baby.

COMMENT

Poisoning by paraldehyde is considered to be a drug idiosyncrasy. The most prominent clinical feature is the profound coma. The postmortem changes are not characteristic.[13]

Bodansky and his associates[14] in their recent studies on the pharmacology and toxicology of paraldehyde reported data which suggest that damage to the liver might play an important role in paraldehyde poisoning.

Doubtless in the case reported here, the element of individual idiosyncrasy to paraldehyde was the deciding factor that caused death. Isolated instances of this sort should not militate against its continued use in medicine and obstetrics, although cognizance should be taken of the possibility of poisoning.

550 Lake Street.

12. Autopsy eport of the coroner of the City and County of San Francisco.

13. McNally, W. D.: Toxicology, Chicago, Industrial Medicine, 1937, p. 671.

14. Bodansky, Meyer; Jinkins, J. L.; Levine, Harry, and Gilbert, A. J.: Anesthesiology 2: 20 (Jan.) 1941.

PLEXIFORM NEUROFIBROMA (VON RECKLINGHAUSEN'S DISEASE) INVADING THE ORAL CAVITY

HAYES MARTIN, M.D., AND CLIFFORD L. GRAVES, M.D.
Attending Surgeon and Assistant Resident, Respectively, Memorial Hospital
NEW YORK

Our purpose in this report is to record 2 cases of bulky plexiform neurofibroma involving the oral cavity and occurring as part of generalized neurofibromatous (von Recklinghausen's) disease. The neurofibromatous tumors which constitute the main characteristic of this disease occur most often in the subcutaneous tissues, and we have been unable to find any report in the literature of bulky intraoral involvement. Small

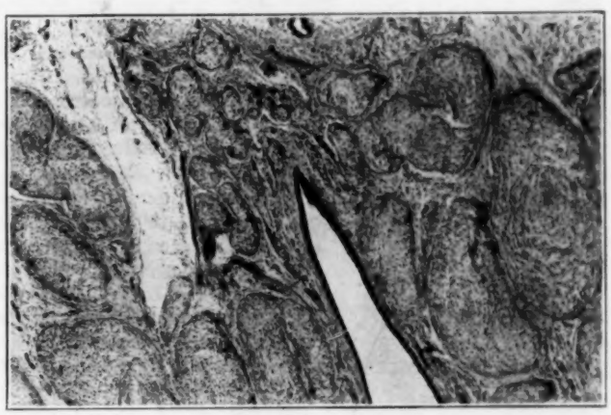


Fig. 1 (case 1).—Section of excised specimen showing plexiform neurofibroma.

isolated fibromas, probably representing the end stage in the organization of pyogenic granulomas, are common in the oral cavity, especially in the mucosa of the cheeks and the tip of the tongue, and should not be confused with these bulky lesions which have a different causation.

Of the 2 cases reported here, the intraoral growth in 1 has remained benign and is only slowly increasing in size. In the other case, the neurofibromatous invasion of the pharyngeal wall and the tongue was associated with a neurogenic sarcoma of the lateral aspect of the neck, and the patient died of local extension of this malignant tumor.

GENERAL CONSIDERATIONS OF VON RECKLINGHAUSEN'S DISEASE

Generalized neurofibromatosis was first described by von Recklinghausen[1] in 1882. He called attention to four major and highly characteristic symptoms and showed that at least three of these have a common pathogenic background: (1) soft cutaneous tumors (formerly called fibroma molluscum); (2) fusiform swelling (neurofibromas) of the nerves; (3) plexiform tumors made up of a network of criss-crossing, anastomosing nerve fibers, and (4) coffee colored areas of pigmentation in the skin (café-au-lait spots).

1. von Recklinghausen, Friedrich: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Festschrift, Berlin, 1882.

Actually, this syndrome had been known long before von Recklinghausen wrote his now famous monograph, but it was his work which first pointed out the derivation of the superficial tumors from the terminal nerve filaments. If, as is now believed by many, the café-au-lait spots are of neurogenic origin, then all four cardinal symptoms can be reduced to a growth perversion of the fetal neuro-ectoderm. The condition known as elephantiasis neuromatosa is closely related.

Fig. 2 (case 1).—Numerous café-au-lait spots are seen on the skin of the back, upper extremities and thighs. Moderate scoliosis of the spine is also shown.

In addition to the syndrome outlined, there are several less obvious manifestations of von Recklinghausen's disease. The condition often exhibits a familial tendency. The patients usually deteriorate mentally as well as physically. They may show various kinds of localized hypertrophies, body asymmetries, developmental defects, endocrine dyscrasias, bony abnormalities, neurotrophic tumors and a variety of bizarre and ill understood phenomena.

The neurofibromas of this disease may occur in the course of nerves anywhere in the body. The most common sites are the subcutaneous tissues of the upper inner surface of the thigh, the inner surface of the upper arm and the posterior surface of the forearm. These lesions are also sometimes found under the mucous membranes of the mouth, the esophagus, the stomach or other parts of the gastrointestinal tract.

INTRAORAL MANIFESTATIONS OF NEUROFIBROMATOSIS

From a review of the literature, it would appear that the mouth is rarely involved in cases of generalized neurofibromatosis. For instance, Bruns [2] in a collected series of 58 cases found only 2 with oral lesions, neither of which was bulky. It is possible that small neurofibromas occur in the mucous membrane of the gastrointestinal tract more frequently than is generally supposed since, when small and asymmetrical, they would escape notice even in the oral cavity unless specifically searched for. As has been previously mentioned, small isolated neurofibromas of the mucous membrane are common benign lesions and are frequently seen in a cancer clinic, where they constitute one of the minor problems in the differential diagnosis of cancer.

The following reports of cases describe bulky involvement of the oral cavity by plexiform neurofibromas in association with generalized neurofibromatosis.

REPORT OF CASES

CASE 1.—*History.*—E. P., a white boy aged 3 years, was first seen in the clinic at the Memorial Hospital in 1932. When he was 4 months old his parents had noticed a prominence of the right side of the jaw which slowly progressed. There was no family history of von Recklinghausen's disease.

Physical Examination.—The general physical and mental development seemed about normal for the patient's age. There were numerous flat, pigmented spots scattered irregularly over the body. The right side of the face presented a diffuse swelling of the soft tissues overlying the mandible from the lobule of the ear to the symphysis menti and extending down into the submaxillary region. This swelling was soft superficially, but at a depth of 2 to 3 cm. there was a nodular, cordlike, more indurated portion. The right lower gum and the floor of the mouth bulged upward and, when palpated, revealed a diffuse submucous indurated swelling. The mucous membrane of the gum was closely attached to the lesion but was movable over the tumor in the floor of the mouth. The tongue was normal. Roentgenograms of the mandible revealed no alteration in bone contour or structure. The blood count was normal and urinalysis and roentgenograms of the chest were negative.

Treatment and Clinical Course.—The oral lesion was recognized as a manifestation of neurofibromatosis and, since there appeared to be no interference with comfort or function, no active treatment was advised at first. During the following two years the local swelling over the mandible and within the mouth increased and became more nodular. The gums on the affected side participated in the general hypertrophy, and the teeth became pushed apart because of a unilateral increase in the size of the mandible. The process within the mouth remained confined to the right side of the midline. In 1934, following the steady increase in size of the local tumor, an attempt was made to excise the submaxillary tumor through an external incision. At the time of operation it was noted that the superficial nerves were numerous and thickened.

The tumor consisted of edematous, soft, lobulated, grayish white tissue which had completely replaced the submaxillary and the sublingual glands. This tissue had also infiltrated the floor of the mouth so widely that its complete removal was impossible. The excised specimen measured 6 by 2 by 2.5 cm. The microscopic diagnosis was plexiform neurofibroma (fig. 1).

Systematic roentgen examinations of the mandible have revealed progressive bone changes. In May 1937 the inferior border of the mandible appeared to be thickened, suggesting osteoma, and in November 1939 roentgenograms showed steady progression of the osteomatous changes and also the appearance of a cystic area in the posterior portion of the horizontal ramus which has slowly advanced, as revealed by later examinations.

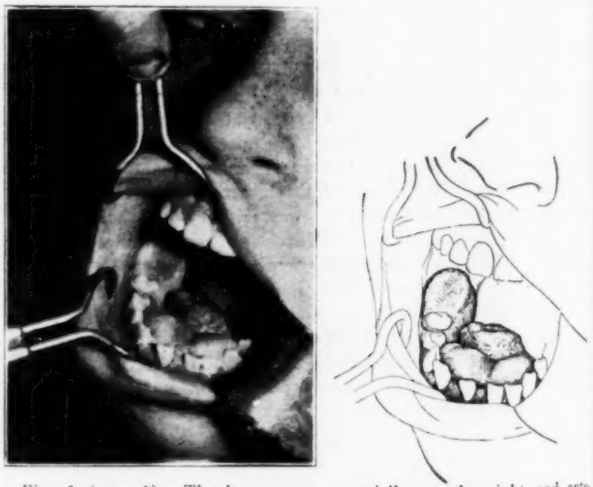


Fig. 3 (case 1).—The lower gum, especially on the right and anteriorly, is considerably thickened, and some of the teeth have been forced outward and apart by expansion of the growth. A separate mass protrudes from the floor of the mouth.

Within the past two years slowly progressing scoliosis has developed, as shown in figure 2. Although there has been a definite, though slow, growth of the tumor of the jaw, its increase in size has not been greatly out of proportion to the

2. Bruns, Paul: Ueber das Renkenneurom, Beitr. z. klin. Chir. **8**: 1, 1891.

boy's general development. At the present writing the appearance is as indicated in figures 3 and 4. There is as yet no evidence of mental deterioration.

CASE 2.—*History.*—D. M., a white girl aged 5 years, was first seen at the Memorial Hospital in October 1939. The

Fig. 4 (case 1).—Diffuse enlargement of the lower right side of the face.

patient's mother, several of the maternal aunts, the maternal grandmother and the great-grandmother were said to have had numerous brown spots on the skin, but as far as could be learned none had had subcutaneous tumors of von Recklinghausen's disease. At the age of 10 months an enlargement was noted on the left side of the child's face. She was taken to a hospital where several roentgen treatments were given, despite which the swelling steadily increased and spread to involve the left side of the neck, the floor of the mouth and the tongue. In the spring of 1939 there was a sudden sharp increase in the size of the external tumor on the side of the neck, and in July 1939 she was operated on at the Presbyterian Hospital in New York. At this operation a well defined bulky tumor mass was found deeply invading the subcutaneous tissue and deep fascial planes, extending from the jugular fossa downward in the left side of the neck. Owing to its deep and widespread infiltration it could not be completely removed. The microscopic diagnosis was "plexiform neurofibroma with areas of sarcomatous degeneration" (fig. 5). The wound healed by primary union, but in two months there was evidence of a recurrence.[3] At this time the child was brought to the Memorial Hospital.

Physical Examination.—The general physical and mental development of the patient appeared to be normal for her age. There were numerous café-au-lait spots scattered over the body. The left side of the face and neck presented a large globular mass 11 cm. in diameter centered about at the angle of the mandible (fig. 6). On examination of the oral cavity, the external mass was found to be continuous with a diffuse submucous involvement of the soft tissues of the cheek, the gums and the left half of the tongue from the tip back to the base and extending into the tonsillar region. The left half of the mandible appeared to be hypertrophied, and the teeth on that side were widely spaced and poorly alined. The lesion did not cross the midline. The soft tissues of the mouth and the subcutaneous tissues of the neck and cheeks were of a rubbery consistency, moderately firm and slightly nodular. Although the skin was movable over the tumor, the mucous membrane seemed rather firmly attached to the lesion within the mouth, but there was no sign of ulceration. There was a recent operative scar 10 cm. long over the upper anterior border of the sternomastoid muscle. The left seventh nerve was partly paralyzed. Routine laboratory tests gave essentially negative results. Roentgen examination of the mandible showed little alteration in contour of the bone except for some pressure atrophy in the region of the coronoid process with subluxation of the temporomandibular joint. Roentgen examination of the lungs showed some elevation of the left side of the diaphragm, presumably from damage to the phrenic nerve in the neck at the time of the attempted operative removal. The skull showed a mild increase in the convolutional markings in the occipital region. The rest of the skeleton was normal.

Treatment and Clinical Course.—The clinical appearance at this time and a review of the histologic slide from the former operation indicated that the resumption of rapid growth under the operative scar was due to a malignant tumor, a neurogenic sarcoma, and that the lesion within the mouth and on the outer surface of the mandible was benign plexiform neurofibroma. Since the recurrent postoperative tumor was inoperable, it was believed that radiation therapy was the only justifiable method of treatment. Over a period of six weeks the patient received fifteen doses of 200 roentgens each to the recurrent tumor in the left side of the neck. The other physical factors were 220 kilovolts, 1.5 mm. of copper filter, 50 cm. target-skin distance, skin portals 9 cm. circular. This treatment was supplemented by the implantation of radon seeds on two occasions for a total dose of 22 millicuries. Although the dose of radiation was great enough to produce a blistering reaction of the skin, it seemed to have little effect on the tumor, which grew steadily, finally producing a bulky necrotic mass shown in figures 7 and 8. The patient died of cachexia and terminal pneumonia approximately one year after the operation and eight months after the beginning of radiation therapy.

Necropsy.—The local tumor invading the soft tissues at the side of the neck extended from about the mastoid region well

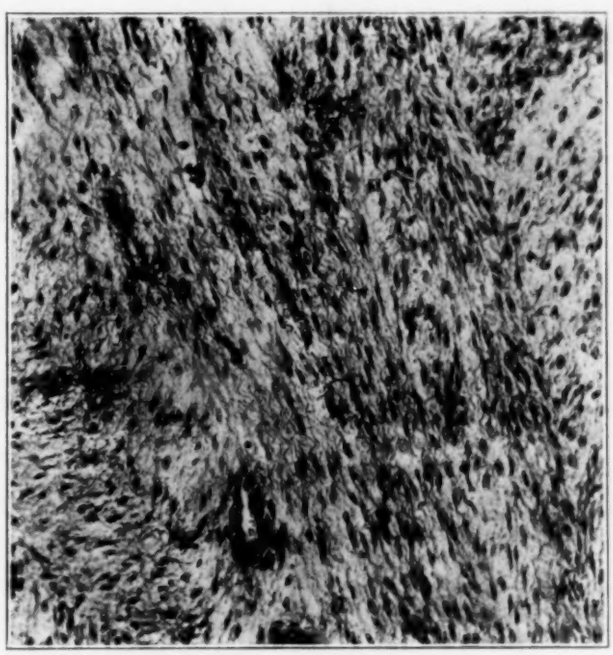


Fig. 5 (case 2).—Section of excised specimen showing plexiform neurofibroma with areas of sarcomatous degeneration.

down into the supraclavicular area. It had invaded and destroyed the mastoid bone, the angle of the mandible, the sternomastoid muscle and the carotid sheath. All the soft tissues in the floor of the mouth were replaced by tumor. The tongue was a shapeless mass completely filling the mouth. The entire tumor measured 25 by 20 by 8 cm. and weighed 2 Kg. Grossly the tumor consisted of glistening white fibrous tissue which

3. Dr. C. D. Haagenson supplied this part of the history.

contained huge numbers of curled up and twisted nerve trunks of all sizes. These trunks after being teased out were not cylindric but rather bulbous, moniliform, beaded and nodular.

There was no evidence of regional or distant metastases. The only other positive finding, beside the extreme emaciation,

Fig. 6 (case 2).—The tumor in the early stages, showing the extensive bulging of the left cheek. The jaws could not be separated widely enough to obtain a photograph of the invasion of the tongue by neurofibromatosis.

was a greatly enlarged liver which reached into the pelvis and weighed 900 Gm. Microscopically the bulk of the liver was due to fatty and degenerative changes without any evidence of tumor invasion.

Microscopically the tumor tissue showed branching and fusing streamers and bundles of oval nuclei on a typically neuromatous

Fig. 7 (case 2).—Anteroposterior view in the terminal stages of the disease, showing the bulky necrotic neurogenic sarcoma.

pattern. In some areas nerve fibers could be identified, but for the most part they had been replaced by tumor tissue. Edema, myxomatous degeneration and liquefaction were widespread. The malignant propensities of the growth were indicated by areas of great cellularity with deep staining nuclei. There were no necrotic areas. The microscopic diagnosis was "pleomorphic neurogenic sarcoma of medium grade."

COMMENT

Both of these patients had unmistakable generalized neurofibromatosis (von Recklinghausen's disease) in addition to their cervical and intraoral tumors. In case 1 there were café-au-lait spots and scoliosis. In this case the symptoms from the intraoral tumor are as yet little more than cosmetic and orthodontic, but it may be expected that the patient will eventually have further complications, either locally from tumor extension or generally from the other effects of this disease. The facial deformity is due as much to a disturbed growth of the parts as to plexiform neurofibromatosis. Since the growth disturbance persists in such cases even though the tumor is removed, the results of operative treatment are always disappointing. The patient is being kept under regular interval observation.

In case 2, the disease ran an entirely different and unique course. The patient had a family background which is generally believed to predispose to early complications. It has been

Fig. 8 (case 2).—Lateral view in the terminal stages of the disease.

observed that when the disease runs through several generations it often has a tendency with each reappearance to occur at an earlier age and to become more severe. As far as we know, an instance of such a fulminating course before the age of puberty has never been reported previously. The tendency toward malignant degeneration in von Recklinghausen's disease is generally recognized. Garré [4] in 1892 reported the incidence as 1.2 per cent. Hoffman [5] in 1910 arrived at the same figure and Hosoi [6] in 1931 reviewed the literature and found it to be 13 per cent. The youngest patient in Hosoi's series was 15 years.

The neurogenic sarcoma in case 2 illustrates several common characteristics of this type of tumor, namely its radioresistance, its failure to metastasize and its locally destructive and invasive characteristics. Stewart and Copeland [7] in an analysis of the clinical material at the Memorial Hospital found that only a small percentage of neurogenic sarcomas are radiosensitive.

4. Garré, Carl: Ueber sekundar maligne Neurome, Beitr. z. klin. Chir. **9**: 465, 1892.
5. Hoffman, J.: L'étude des théories actuelles sur la neurofibromatose et ses complications, Thése de Genève, 1910.
6. Hosoi, Kiyoshi: Multiple Neurofibromatosis, with Especial Reference to Malignant Transformation, Arch. Surg. **22**: 258 (Feb.) 1931.
7. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer **15**: 1235 (July) 1931.

In Hosoi's series there were metastases in only 22 per cent of the cases. The rapid growth and destructiveness of the tumor in our case 2 is characteristic of all malignant tumors in childhood as compared to their anatomic and histologic counterparts in the adult.

Plexiform neurofibromas, although histologically benign, are always infiltrating and invasive tumors which cross tissue planes and anatomic boundaries, a fact which is well illustrated in both cases recorded in this report. Despite this invasive capacity it is noteworthy that in neither instance did the lesion cross the midline. This peculiarity is well illustrated by case 1, in which the invasion of the mandible, the gum, the floor of the mouth and the tongue has not passed the midline. In case 2 the lesion remained unilateral until the tumor assumed a rapidly growing invasive quality during the last few months of life. Müller [8] has collected 4 cases of "macroglossia neuromatosa unilateralis" and added 1 of his own.

SUMMARY

In the 2 cases of generalized neurofibromatosis here reported there was bulky invasion of the oral cavity. Both of these occurred in children with involvement of the subcutaneous tissues, the bone and the soft tissues of the gum, the floor of the mouth and one side of the tongue. In 1 case the disease appears to be only slowly progressing and benign. In the second case the local tumor took on malignant, locally invasive characteristics and caused death. The autopsy revealed no sign of general dissemination.

737 Park Avenue.

8. Müller, Hans: Makroglossia neurofibromatosa congenita, Centralbl. f. allg. Path. u. path. Anat. **57**: 55 (March 20) 1933.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

THEODORE G. KLUMPP, M.D., Secretary.

ALUMINUM HYDROXIDE GEL.—An aqueous suspension containing not less than 3 per cent nor more than 4.2 per cent of aluminum oxide, chiefly in the form of aluminum hydroxide. Flavoring, sweetening and preservatives may be added.

Actions and Uses.—Aluminum hydroxide gel has been shown to be an effective gastric antacid and neutralizes hydrochloric acid of the stomach by chemical reaction. It does not increase the p_H of the gastric juice beyond the point which interferes with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization, which are the principal disadvantages of ordinary alkalis. The amphoteric nature of aluminum hydroxide gel is not of clinical significance because it reacts as an acid only in fluids with a p_H above 9: such a p_H is not encountered in the gastrointestinal tract. Its so-called buffer action occurs only at a p_H of about 4. It is presumed that the acid salt aluminum chloride, which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach, is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine, and the chloride is reabsorbed. Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Some evidence also suggests that its effectiveness may be further explained by the tendency to increase mucin secretion and the ability to precipitate pepsin in vitro. See also the general article, Aluminum Compounds, New and Nonofficial Remedies, 1941, page 53.

As with other aluminum compounds, aluminum hydroxide is not absorbed from the gastrointestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Its astringent property may produce a constipating effect.

There is evidence available to suggest that administration of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency in the presence of a relative or absolute pancreatic deficiency, diarrhea or low phosphorus diet by combination with phosphates in the intestinal tract. This objection does not affect its usefulness in uncomplicated peptic ulcer and gastric hyperacidity, since the diet employed in these conditions is ordinarily relatively rich in phosphorus. Aluminum hydroxide gel may possess adsorptive properties, but specific conclusive evidence that acid, toxins, bacteria or gases are absorbed is lacking, and in the case of hydrochloric acid is opposed by in vitro evidence to demonstrate that its reaction with this substance is completely accounted for on the basis of simple chemical neutralization.

Aluminum hydroxide gel is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage in this condition and for the control of symptomatic gastric hyperacidity only. Its oral or rectal use in the treatment of other gastrointestinal conditions is not adequately supported by existing clinical evidence.

Dosage.—Aluminum hydroxide gel is administered orally in doses of from 1 to 2 drachms (4 to 8 cc.) in one-half glass of water or milk every two or four hours, or one-half to one hour after meals. It may be administered by the method of continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33⅓ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1,500 cc. of diluted suspension per twenty-four hours.

Creamalin.—A brand of aluminum hydroxide gel-N. N. R. The preparation contains 5.5 per cent aluminum hydroxide (equivalent to 3.3 per cent aluminum oxide). Oil of peppermint is added as a flavoring agent. Marketed in bottles of 3, 6 and 12 fluidounces.

Manufactured by Alba Pharmaceutical Co., Inc., New York. No U. S. patent. U. S. trademark 353,596 (registered Feb. 15, 1938).

Aluminum hydroxide gel occurs as a white or light gray suspension which may settle out to some extent or form a semisolid on standing but which liquefies on shaking. The specific gravity at 25 C. is from 1.030 to 1.042.

Transfer about 5 Gm. of aluminum hydroxide gel to a glass container and add 10 cc. of diluted hydrochloric acid: the solution is clear and colorless within ten minutes; to this solution add 8 cc. of ammonia water: a flocculent precipitate appears which is insoluble in excess ammonia water but soluble in sodium hydroxide solution. To about 5 Gm. of aluminum hydroxide gel in an Erlenmeyer flask add 10 cc. of sodium hydroxide solution and boil: the fumes do not turn moistened red litmus paper to blue (*ammonia*).

Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted hydrochloric acid and boil. Cool, dilute to 250 cc. and filter if necessary. To 10 cc. add 1 cc. of barium chloride solution and allow to stand for ten minutes: the turbidity is not greater than that produced by 0.2 cc. of fiftieth-normal sulfuric acid in 10 cc. of water.

The p_H at 25 C. of aluminum hydroxide gel is between 6.4 and 7.2. Dissolve 2.5 Gm. of the gel in 5 cc. of diluted sulfuric acid and boil: the solution meets the U. S. P. XI test for arsenic. Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted sulfuric acid: the resultant solution conforms to the U. S. P. XI test for heavy metals.

Transfer 25 Gm. of aluminum hydroxide gel, accurately weighed, to an Erlenmeyer flask, add 25 cc. of distilled water and 0.2 cc. of potassium chromate solution. Titrate with tenth-normal silver nitrate to a faint pink color: the chloride content is not greater than 0.25 per cent.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed, to an Erlenmeyer flask, dilute to 30 cc. and maintain at 37.5 C. Titrate with tenth-normal hydrochloric acid during forty minutes, adding the acid in 0.5 cc. portions toward the end of the titration, using bromphenol blue as indicator: the volume of tenth-normal acid used is not more than 2,500 cc. nor less than 1,250 cc. per hundred Gm.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed, to a 250 cc. beaker and dilute to 100 cc. Add 10 cc. of diluted hydrochloric acid, heat to boiling and make the mixture alkaline to methyl red with ammonia water. Dilute to 200 cc., heat to boiling and wash four times by decantation. Filter and wash the precipitate free of chlorides with an aqueous solution containing 1 part of ammonia water in 25 parts of solution. Dry the precipitate and ignite at 900 C. to constant weight: the aluminum oxide content is not less than 3 nor more than 4.2 per cent.

THIAMINE HYDROCHLORIDE-U. S. P. (See New and Nonofficial Remedies, 1941, p. 551).

The following dosage form has been accepted:

Solution Thiamine Hydrochloride-Upjohn, 50 mg. per cc., 10 cc. vial: Each cubic centimeter contains 50 mg. of thiamine hydrochloride, equivalent to 16,667 U. S. P. units, and 5 mg. of chlorobutanol in sterile distilled water.

Prepared by the Upjohn Company, Kalamazoo, Mich.

RIBOFLAVIN (See New and Nonofficial Remedies, 1941, p. 553).

The following dosage form has been accepted:

Tablets Riboflavin-I. V. C., 1 mg.

Prepared by International Vitamin Corporation, New York.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - - CHICAGO, ILL.

Cable Address - - - - "Medic, Chicago"

Subscription price - - - - - Eight dollars per annum in advance

Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.

SATURDAY, NOVEMBER 1, 1941

ARMY MORALE AND THE MEDICAL RESERVE CORPS

Recently much has been written about morale, an invisible and intangible factor which, like a vitamin, a ferment or a hormone, has vast potentialities. The United States Army in supervising and directing the habits and lives of over a million of our young men of impressionable age is not only building a fighting force but shaping the morale of this nation for years to come.

Various definitions have been used to describe the elusive nature of morale. A playwright in a recent popular play [1] had his hero call it "a dirty French word." The outgoing chief of the Morale Branch of the Army,[2] preferred the definition "a state of mind with reference to confidence, courage, zeal and the like—especially of a number of persons associated in some enterprise, as troops." A philosopher [3] with Army World War experience used various terminologies. A psychologist [4] who was a morale officer in the World War recently emphasized that morale had its basis in physical and economic well-being in addition to mental fitness, while a science writer [5] set out four attributes of morale, with emphasis on physical well-being. Gulick [6] called it "the quality of the spirit of the whole," an Army officer [7] with World War morale experience depicted it as "a science involving a number of sound principles of psychology applied to the everyday life of the soldier." The chief of the Morale Branch of the Army [8] in the last World War decided that "morale is a term which should be used to express the measure of determination to succeed in the purpose for which the individual is trained or for which the group exists."

Only recently President Roosevelt affirmed the present importance of morale with the observation "we are only as strong as our morale," [9] and experts on morale have been showering our legislators and our press [10] with suggestions that something be done on a national scale to mobilize and direct our national morale, be it civil or military.

Rumors and impressions concerning lack of proper morale in the United States Army have been spread over the pages of newspapers and surveys have been made and published by *Life* and *Time* magazines. The recent appointment of Frederick Osborn, New York financial leader, scientist and humanitarian, to be brigadier general in the Army, in charge of the Morale Branch, has already stimulated interest in improved Army morale. Some veteran newspaper reporters who saw the Nazi army in action in Europe and who recently saw the American Army on maneuvers state that even now the United States Army "has the edge" on the Germans in morale.[11]

The medical profession has a large concern in the question of Army morale. On the shoulders of 9,950 physicians now in active service [12] as medical officers in the Army rests a large part of the burden of keeping the soldiers mentally and physically healthy. Of this total, 8,700 medical officers have been drawn from the Medical Reserve Corps, while 1,250 are regular Army medical corps officers. The importance of the morale of these medical officers directly and indirectly might well cause the War Department some concern, since the attitude of the reserve medical officers now on active duty has been seriously affected by a policy recently adopted.[13] This policy provides that promotions above the grade of Major are temporarily suspended as far as reserve officers are concerned. The Medical Reserve has existed for thirty-three years. It was the first reserve corps created in the United States Army.[14] Reserve corps were unknown in any other branch of the Army until 1916.

How can the policy makers in the War Department expect a doctor to have "a state of mind with reference to confidence, courage, zeal and the like" when he

1. Brennan, Frederick Hazlitt, The Wookey, 1941.
2. Ulio, Brig. Gen. James A.: Building Military Morale, Hygeia **19:** 792 (Oct.) 1941.
3. Hocking, W. E.: Morale and Its Enemies, New Haven, Yale University Press, 1918.
"Morale is the practical virtue of the will to war." p. ix.
"In no war, I judge, has the human quality counted for so much:—the endurance, the initiative, the power of sacrifice, the loyalty, the ability to subordinate personal interest and pride, the power of taking the measure of the event, of discounting the unfavorable turn, of responding to frightfulness with redoubled resolution rather than with fear, of appreciating the real emergency and rising constantly to meet it. It is these qualities of mind and character which in the ensemble go by the name of 'morale'; and it is these qualities that hold the balance of power in war." p. 8.
"Morale wins, not by itself, but by turning scales; it has a value like the power of a minority or of a mobile reserve. It adds to one side or the other the last ounce of force which is to its opponent the last straw that breaks its back." p. 9.
"What 'condition' is to the athlete's body, morale is to the mind. Morale is condition. . . ." p. 14.
4. Fryer, D. H., quoted in Science News Letter **39:** 101 (Feb. 15) 1941.
5. Van de Water, M.: Morale Defense, Science News Letter **39:** 330 (May 24) 1941. The author sets out the elements of morale as (1) physical well-being (good health), (2) mental well-being (freedom from worry), (3) confidence in leadership, (4) recognition of the individual.
6. Gulick, L. H.: Morals and Morale, New York, Association Press, 1919, p. xi.
7. Miller, A. H.: Leadership, New York, G. P. Putnam's Sons, 1920, p. 4.
8. Munson, Brig. Gen. E. L.: The Management of Men, New York, Henry Holt & Co., 1921, p. 3.
9. Message to Defense National Recreation Congress, Baltimore, Sept. 29, 1941.
10. Perry, R. P. (professor of philosophy, Harvard University): Letter to New York Times, Sept. 2, 1941. Pope, A. A. (chairman of Committee for National Morale): Letter to New York Times, Sept. 26, 1941.
11. Kay, L., and Hottelet, R. C.: United Press dispatch dated Sept. 30, 1941 from Shreveport, La.
12. War Department figures as of Sept. 27, 1941.
13. Press Release, War Department, dated Aug. 29, 1941.
14. Hume, E. E.: Training of Medical Officers for War Duty, War Medicine **1:** 624 (Sept.) 1941.

spends a number of years in the Medical Reserve Corps, is called from his practice to active duty and finds that it is impossible for him to secure a promotion above the rank of Major, no matter what his service or what his ability? Perhaps the new chief of the Morale Branch of the Army, under his powers to investigate and recommend morale-building factors to the General Staff, will investigate the morale-destroying effect of this newly adopted policy.

None of the reserve officers expect promotion over the heads of regular Army officers, but reserve officers who merit advancement should not be routinely held back. Promotion of reserve officers is now provided for by a ruling of the Adjutant General[15] which sets forth the requirements for obtaining a "Certificate of Capacity" which is necessary before a reserve officer can be promoted to a higher grade. This regulation requires a year of active duty with an efficiency rating of at least "satisfactory" for grades up to and including that of Major, and of "excellent" for grades of Lieutenant Colonel and Colonel. This limitation on promotion is fair and should be the only limitation, provided the reserve officer's age and experience warrant a higher rank.

AIR BORNE INFLUENZA VIRUS

The extent to which infectious agents pass from the respiratory tract of one host to that of another through the air has been frequently investigated. William F. and Mildred W. Wells[1] have emphasized the possible importance of "droplet nuclei," ultramicroscopic particles resulting from the evaporation of expelled spray. Such nuclei are little influenced by gravity and may carry viable bacteria in the air for many hours. Wells and Brown[2] have demonstrated the prolonged viability of the influenza virus in the air. Now further important experimental evidence along these lines has recently been reported by Andrews and Glover[3] of the National Institute for Medical Research in England.

The British investigators exposed normal ferrets in a closed room to ferrets experimentally inoculated with influenza A virus. Each room was about 6 by 6 by 9 feet high and was provided with a window facing the door. Before each experiment the walls, ceiling and floor of each room were washed down with saponated solution of cresol followed by water from a high pressure hose. The attendants wore rubber boots and mackintoshes wet with cresol solution and otherwise adopted meticulous antiseptic precautions. In most experiments two infected "donors" were placed in a single open wire meshed rabbit cage near the floor on one side of the room, while the two normal "recipients" were placed in two separate cages on the opposite side of the room and about 3 feet above the "donors." In certain experiments a plywood screen was placed between the donor and the recipient in order to minimize the possibility of direct droplet transfer.

In their initial experiments 21 normal ferrets were exposed at a horizontal distance of 5 feet to 19 infected donors. After an exposure of from four to seven days 13 of the normal ferrets developed typical fever (104.6 F. or higher) and nasal symptoms, and in all cases the diagnosis was confirmed by a subsequent immunity test with homologous influenza virus. Aerial transmission of infectious doses of the influenza virus is therefore readily effected in closed rooms, the direct projection of nasal spray presumably being of minor importance. In control experiments in which the window was left open so as to increase ventilation, cross infection did not take place despite seven days' exposure to the infected air.

The idea that infectious particles may spread by means other than droplet transfer was further confirmed by successful infection of normal ferrets through S shaped or U shaped ventilation shafts, the cages being so planned that, at the low air speed employed, gross particles presumably would not be carried around the right angle turns but would impinge on the walls and be trapped. In all experiments by this technic 100 per cent takes were recorded after from five to seven days' exposure to the contaminated air currents.

Of equal hygienic interest are Glover's[4] tests of the possible aerial transmission of a double streptococcic influenzal infection. Ferrets simultaneously inoculated with influenza A virus and group C streptococcus usually exhibit fatal respiratory symptoms, necropsy revealing intense hemorrhagic reactions of the nasal mucosa with a plum colored congestion involving nearly the whole of both lungs. Such ferrets give off both virus and streptococci into the air, blood-agar plates exposed at a distance of 4 feet usually developing in the neighborhood of one hundred colonies of group C streptococcus per plate after three hours' exposure.

The double infection is readily transferred by contact to normal ferrets placed in the same cages with doubly infected donors. When the animals are separated by an air barrier of 4 feet, however, the streptococci fail to be transferred, only a relatively mild air borne virus infection being demonstrable. Apparently air borne streptococci are unable to establish themselves on the normal nasal mucosa. If, however, ferrets previously infected with the influenza A virus are substituted for the normal recipients, a superimposed air borne streptococcic infection usually develops. This predisposing damage to the nasal mucosa may be specific, as chemical agents have thus far failed to produce the necessary local nasal potentiation.

---

15. AG210.2 ORC (5-31-41).

1. Wells, William F., and Wells, Mildred W.: Air Borne Infection, J. A. M. A. **107**: 1698 (Nov. 21), 1805 (Nov. 28) 1936.

2. Wells, W. F., and Brown, H. W.: Recovery of Influenza Virus Suspended in Air, Science **84**: 68 (July 17) 1936; Am. J. Hyg. **24**: 407 (Sept.) 1936.

3. Andrews, C. H., and Glover, R. E.: Brit. J. Exper. Path. **22**: 91 (April) 1941.

4. Glover, R. E.: Brit. J. Exper. Path. **22**: 98 (April) 1941.

Current Comment

CANCER MORTALITY DECLINES IN NEW YORK

The division of cancer control of the New York State Department of Health has announced a decrease in cancer mortality in upstate New York.[1] This decrease is most definite among women aged 25 to 45, in whom a decrease of 10 per cent was noted between 1930 and 1940. In the same period a decrease of approximately 3 per cent occurred in older women. The cancer mortality among men at all ages increased, but this increase was limited to men over 44; in men aged 25 to 44 the rate remained practically unchanged. Changes in the age distribution of the population were sufficient to increase the cancer mortality among males by 14 per cent from 1930 to 1940, in addition to a so-called true increase of 9 per cent, a total of 23 per cent. In women, changes in age distribution should have increased the cancer rate by 12.2 per cent, whereas actually this rate increased by only 8.6 per cent, or a "true" decrease in the cancer mortality among women of 3.6 per cent. Decreases in cancer mortality are particularly significant because they represent a reversal of the upward trend which this rate has pursued consistently for more than half a century. Taken over an eleven year period it is of more significance than are year to year fluctuations. In conjunction with the cancer reporting law [2] the hope expressed in the press release [1] is particularly significant:

> The decrease in cancer mortality among women undoubtedly is due to more early diagnosis and effective treatment, especially of cancer of the breast and uterus. In women, these are the two most frequent forms of cancer, accounting for over a third of all deaths from cancer. At the same time they are readily discovered at an early stage and treatment is highly effective. The decrease in cancer mortality among women, which is now a fact, can probably be continued and intensified in the next ten years.

WEIGHT REDUCTION DIETS

On the street and particularly on the beach are visible the "overweights." In some countries obesity is considered a desirable attribute, but not in this country at this time. Recently, perhaps owing to the change to more revealing clothes, the American public has become "figure conscious." In every public conveyance, in newspapers and magazines and on many a daytime radio program the idea of "the form divine" is hammered into our consciousness. Unquestionably Hollywood has exerted its influence in this regard through the heroines and glamor girls who exhibit their attributes to millions of fascinated eyes. To photograph well they must be thinner than they wish to appear. In years past "Hollywood" reducing diets were promoted, the implication being that the Hollywood diet would produce a Hollywood figure. For the most part, these diets were unscientific; sometimes they were dangerous. Recently several magazines with a combined circulation of many millions have been publishing diets for reduction of weight. For the most part these diets furnish from 1,000 to 1,500 calories daily and have been planned by persons well trained in dietetics. What attitude should physicians assume toward these diets? Shall we say that the diets are unscientific or dangerous? That would not be true. Should we state that people should never follow a reducing diet without a physician's advice? The magazines themselves urge this. Or should the profession realize that one reason why such dietary suggestions are in demand is because patients have had difficulty in obtaining these diets from their physicians? How many physicians have neglected the importance of diet in the treatment of the patient? "Doctor, I'm overweight. What would you suggest?" "Oh, I'd cut down on the fats, starches and sweets." Why shouldn't this patient welcome some real help from a magazine article? How much time is spent in the curriculum of the medical school in instructing students in the planning of diets? These recently published diets are not those of the dietary faddist. They do not contain the "screw-ball" teachings of William Howard Hay or Bengamin Gayelord Hauser. In general, the diets are excellent. Some may not contain all the protein that they should, and many still require vitamin supplements. But the only good answer that a physician can make to one of these diets is his ability to plan a better one.

1. News Service Release, New York State Department of Health, Albany, Oct. 1, 1941, Edward S. Godfrey Jr., M.D., commissioner.
2. Experiments in Cancer Reporting, Current Comment, J. A. M. A. **115:** 136 (July 13) 1940.

DIET AND CIRRHOSIS OF THE LIVER

The relation of dietary protein to health and disease was stressed recently in THE JOURNAL,[1] and reference was made to the observation that protein fed to protein depleted dogs may protect them from liver injury due to chloroform anesthesia. A similar important role of dietary protein is seen in a recent report [2] from the United States Public Health Service. Rats on a low protein ration contracted cirrhosis of the liver in the course of a year following the initiation of the experiment. Another group of animals on the same diet received a 20 per cent solution of alcohol to drink freely in place of water. In this group of rats pathologic liver changes developed which were, on the whole, more severe than in the first group. In two other series of rats on an adequate protein diet, one receiving water and the other 20 per cent alcohol to drink, there were no pathologic changes in the liver. The low sulfur content of the protein poor ration employed suggests a relationship of amino acid content of the diet to the ability of the liver to withstand the toxic effects of orally administered poisons. This view would appear to be in harmony with two known metabolic roles of certain amino acid constituents of proteins; namely, in detoxication mechanisms available to the organism and in promoting the regeneration of injured tissue by providing an adequate supply of the constituents from which new tissue protein is made.

1. Dietary Protein and Its Relation to Health and Disease, editorial, J. A. M. A. **117:** 113 (July 12) 1941.
2. Lillie, R. D.; Daft, F. S., and Sebrell, W. H., Jr.: Cirrhosis of the Liver in Rats on a Deficient Diet and the Effect of Alcohol, Pub. Health Rep. **56:** 1255 (June 13) 1941.

MEDICAL PREPAREDNESS

In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.

EXAMINATIONS FOR APPOINTMENT TO NAVY MEDICAL CORPS

Examinations for appointments as acting assistant surgeon for intern training effective on completion of their medical course will be held for all applicants of the senior classes of class A medical schools on Jan. 5 to 9, 1942 inclusive at all of the larger U. S. naval hospitals within the continental limits of the United States. Prospective candidates should communicate with the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., for full information and application forms.

An acting assistant surgeon who has served as an intern in a U. S. naval hospital for twelve months may apply for appointment as assistant surgeon, rank of lieutenant (junior grade), Medical Corps, U. S. Navy, in the regular Navy, or may apply for appointment as a lieutenant (junior grade), Medical Corps, Volunteer General Service Class, U. S. Naval Reserve, and be continued on active duty during the continuation of the present emergency.

The examination for appointment as assistant surgeon, lieutenant (junior grade), Medical Corps, U. S. Navy, will also be held on Jan. 5 to 9, 1942 inclusive at all larger naval hospitals for candidates who are graduates of class A medical schools and who have, or will have within the next four months, completed an internship of twelve months' duration in a hospital accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association. Interested persons should apply to the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., for full information and application forms.

It is planned to have examinations for appointment as acting assistant surgeons and as assistant surgeons, U. S. Navy, during the months of January, May, August and October of each year, the exact dates to be announced by the Surgeon General of the Navy.

Applicants for appointment in the Medical Corps of the regular Navy are required to be less than 32 years of age at the time of their appointment. The maximum age limit for appointment in the Medical Corps of the Naval Reserve is "50 years of age."

MEDICAL STUDENTS

Junior and senior medical students in good standing in class A medical schools are eligible for appointment as ensigns in the volunteer probationary class H of the Naval Reserve.

Ensigns, T.-V.(P.), U. S. Naval Reserve, on successful completion of their junior year of medicine, as well as all other medical students in similar status, may apply for and be examined for appointment as acting assistant surgeon (intern), U. S. Navy. Such appointments will become effective following their graduation from medical school.

Ensigns, H.-V.(P.), U. S. Naval Reserve, who do not qualify for appointment as acting assistant surgeon (intern), U. S. Navy, are reappointed, on graduation, lieutenants, junior grade, in the volunteer general service class of the Naval Reserve. It is the present intention of the Bureau of Medicine and Surgery to have such medical officers complete one year's internship before nominating them for active duty assignments.

All applications for appointment as ensign, H.-V.(P.), U. S. Naval Reserve, are required to be filed with the commandant of the naval district in which the applicant resides.

THE NEW NAVY MEDICAL CENTER

The Navy Medical Center at Washington, D. C., will move within the next few months to a 250 acre tract just north of Bethesda, Md., where work on a group of new buildings has been going on since July 1939. The new buildings of the Navy Medical Center comprise the main administration building, officers', nurses' and hospital corpsmen's quarters, ward buildings, power plant, laundry and garage. The administration building is impressive, having a tower rising 270 feet above the ground level and twenty stories high. President Roosevelt himself has taken an active part in the architect's drawing and general plans of the building. The main building has a frontage of 266 feet, with three story wings extending 158 feet. Nine floors of the tower will be used also for officer patients and four floors of the tower for enlisted patients. The bed capacity at present is 500 but this will be increased by the addition of wings. A harmonious effect in the various rooms and corridors is produced by the use of terra cotta tile of various colors, and the lobby is lined with marble and trimmed with white bronze.

The main building contains the Navy medical and dental schools, laboratories, libraries, photographic, multigraphing and conference rooms and the entire library of the Surgeon General of the Navy, which is said to be the largest and most important collection of material on naval medicine in the world. The center contains also an auditorium seating five hundred and ninety-six. The main operating room, on the second floor, is lined with Tennessee marble and has a glass enclosed viewing gallery.

The medical school has complete research laboratories. This is a postgraduate school, where young physicians who are graduates of accredited medical schools receive intensive training in medicomilitary subjects, tropical diseases and the problems of submarine and aviation activities being particularly stressed. The actual project of construction of the new school has been carried out under the general direction of Rear Admiral Ross T. McIntire and by the chief of the Bureau of Yards and Docks, Rear Admiral Ben Moreell of the Civil Engineer Corps, U. S. Navy.

NEW NAVY HOSPITALS AND DISPENSARIES

The Secretary of the Navy announced October 15 that the Bureau of Medicine and Surgery of the Navy is bringing to completion new navy hospital facilities which are in keeping with the navy's expansion into a two ocean navy. Following are the new naval hospitals:

NEW NAVY HOSPITALS

(*a*) U. S. Naval Hospital at Aiea, near Pearl Harbor, T. H., is under construction, at a cost of $2,600,000. The hospital will provide 400 beds, with major hospital facilities. In connection with the hospital is a new naval medical supply storehouse.

(*b*) U. S. Naval Hospital, Long Beach, Calif. A 300 bed hospital, costing $2,500,000 and with major hospital facilities, is to be built at Long Beach. Plans are being completed for this institution.

(*c*) U. S. Naval Hospital, Key West, Fla. Plans are being completed for a 150 bed hospital of permanent construction, at a cost of $1,000,000.

(*d*) U. S. Naval Hospital, Coco Solo, C. Z. Under construction is a 150 bed hospital with complete facilities at a cost of $1,100,000.

(*e*) U. S. Naval Hospital, Balboa, C. Z. A temporary type hospital of 120 beds is under construction at a cost of $750,000.

(*f*) U. S. Naval Hospital, Quantico, Va. On July 1, 1941 the former post-sick quarters became a naval hospital by congressional legislation.

(*g*) U. S. Naval Hospital, Charleston, S. C. Under a grant of $645,000, the new naval hospital at Charleston will be completed. The capacity will be 200 beds. The hospital was begun in 1940 as a WPA project.

(*h*) U. S. Naval Hospital, Jacksonville, Fla. The 200 bed hospital facility at the Naval Air Station, Jacksonville, was officially designated as a naval hospital on July 1, 1941. The hospital is of temporary construction and provides major hospital facilities.

(*i*) U. S. Naval Hospital, Corpus Christi, Texas. The 400 bed hospital facility at Corpus Christi was officially designated as a naval hospital on July 1, 1941.

(*j*) U. S. Navy Medical Center, Bethesda, Md. (Washington, D. C.). The 500 bed Navy Medical Center is nearly completed at Bethesda, Md.

(*k*) U. S. Naval Hospital, Pensacola, Fla. The new hospital at the Naval Air Station is nearly completed. About 200 beds will be provided.

DISPENSARIES AND HOSPITAL FACILITIES

(*a*) Naval Air Station, Argentia, Newfoundland. A dispensary of 150 beds with hospital facilities is to be constructed immediately at a cost of $500,000.

(*b*) Marine Corps Base, New River, N. C. A post-sick quarters of 200 beds will be constructed with complete hospital facilities.

(*c*) Marine Corps Aviation Base, Neuse River, N. C. A post-sick quarters of 200 beds will be built. Complete aviation medical and hospital facilities will be provided.

(*d*) Naval Operating Base, Norfolk, Va. A modern 150 bed dispensary will be built at the Naval Training Station, Norfolk, at a cost of $375,000.

(*e*) Naval Station, Tutuila, Samoa. A modern dispensary of 50 beds will be constructed at Tutuila at a cost of $180,000.

(*f*) Naval Station, Charlotte Amalie, Virgin Islands. A 30 bed modern dispensary is under construction at a cost of $145,000.

(*g*) Naval Air Station, Barber's Point, T. H. A 150 bed dispensary will be constructed at a cost of $400,000.

(*h*) Naval Air Station, Quonset Point, R. I. A dispensary of 100 beds is nearly completed.

(*i*) Naval Air Station, San Juan, P. R. A modern 44 bed dispensary is under construction.

(*j*) Naval Air Station, Alameda, Calif. A dispensary of 100 beds is under construction.

(*k*) Naval Air Station, Kodiak, Alaska. A modern dispensary of 100 beds is under construction.

(*l*) Naval Air Station, Kaneohe, T. H. A modern dispensary of 100 beds is under construction.

(*m*) Naval Air Station Trinidad. A dispensary of 150 beds will be built.

(*n*) Naval Air Station, Unalaska, Alaska. A dispensary of 120 beds, with hospital facilities, will be built at a cost of $575,000.

MEDICAL SUPPLY DEPOTS

(*a*) Brooklyn. Under a recent appropriation of $600,000, the Brooklyn Medical Supply Depot will be further extended along High Street.

(*b*) Newport, R. I. A medical supply storehouse will be built at a cost of $200,000.

(*c*) Oakland, Calif. A large naval medical supply depot is nearly completed.

(*d*) Pearl Harbor, T. H. In connection with the new naval hospital at Aiea, a medical supply storehouse is under construction at a cost of $275,000.

HOSPITAL CORPS TRAINING SCHOOLS

In connection with the program of providing trained medical personnel for the augmented Navy, a new Hospital Corps Training School with a capacity of 400 students will be constructed at Great Lakes, Ill., and the existing schools at Norfolk and San Diego will be increased.

EXPANSION OF EXISTING NAVAL HOSPITALS

(*a*) U. S. Naval Hospital, Chelsea, Mass. A new wing of about 90 beds is under construction at a cost of $250,000.

(*b*) U. S. Naval Hospital, Philadelphia. A large supply storehouse is under construction, costing $100,000.

(*c*) U. S. Naval Hospital, Annapolis, Md. A new wing is being added at a cost of $475,000.

(*d*) U. S. Naval Hospital, Quantico, Va. An isolation ward building is under construction at a cost of $65,000.

(*e*) U. S. Naval Hospital, San Diego, Calif. New sick officers' quarters and outpatient clinic will be built at a cost of $275,000.

(*f*) U. S. Naval Hospital, Mare Island, Calif. A new wing is under construction, costing $475,000.

(*g*) U. S. Naval Hospital, Puget Sound, Wash. A new galley and mess hall and a ward wing are under construction, at a total cost of $725,000.

ARMY COLD WEATHER HEADGEAR

The results of experiments on clothing for cold climates made during the Byrd Antarctic expeditions have been used in the designs of new headgear for soldiers, standardized by the Army Quartermaster Corps, the War Department has announced. An olive-drab knitted cap, a stocking cap and a cloth hood, designed for protection of the head and neck, will be used by soldiers this winter.

Adapted from the Eskimo parka for Army use, the hood is made of wind and water resistant poplin. Tightening a drawstring brings the hood together in front to cover almost the entire face. The attached shawl protects the back of the soldier's head and fits down over the top of his shoulders.

The new cap, which may be worn up over the ears, includes a snug shawl which may be turned down when necessary to protect the ears and neck.

During his Antarctic experiments, Dr. Paul Siple developed a formula to measure the effects of wind on the heat loss of the body. He found that, whereas a person wearing only a medium heavy sweater is reasonably warm at zero temperature, he quickly becomes cold if there is a wind of even 10 miles an hour velocity, because his heat loss increases in proportion to the increase in the velocity of the wind.

SPARKPROOF SHOES FOR ARMORED TROOPS

Sparkproof shoes are among the latest types of footwear being tested by the Army. The new shoes are designed for soldiers who dispense gasoline and other inflammable materials, particularly in the Armored Force, where a spark may be disastrous.

Vulcanized fiber instead of metal is being used for washers in the heels of these new shoes, and the nails are made of a nonsparking metal. Shoes made according to this new design are being given a thorough workout by soldiers of a gasoline and oil battalion in the Armored Force. If they prove satisfactory, all soldiers who perform duties in which a spark may be dangerous will be provided with these sparkproof shoes.

BUILDING UP A BLOOD PLASMA BANK

The American Red Cross is conducting a program to build up a blood plasma bank for use of the military forces with sufficient reserve for civilian catastrophe aid. The program already has been established in seven cities and will soon be expanded to a total of twenty-two chapters. The American Red Cross has already completed a bank of 15,000 blood plasma units and expects to build the initial bank to 200,000 units. Capt. Charles S. Stephenson, Medical Corps, U. S. Navy, has just completed a tour of inspection of the medical and research centers of England made in cooperation with the National Research Council, the Medical Research Council of Great Britain and Canadian research organizations. In his report to the Secretary of the Navy, Captain Stephenson said that the use of dried blood plasma for emergency administration to patients in the field suffering from traumatic shock and loss of blood has been highly effective in saving life. He further stated that the biologic laboratories of the United States have equipment for preparing dried plasma and are now preparing several hundred packages each week and will be able within a month to process several thousand quarts of blood each week. The real problem in the United States, he said, is to develop a sufficiently large list of blood donors to permit this work to be carried on effectively. Dried plasma is packaged by the biologic laboratories with the proper amount of distilled water to restore the essential fluidity, and it is then available for immediate use either in hospitals or in the midst of battle or bombing raids of cities.

RED CROSS TO TEACH HOME NURSING

The American Red Cross classes in home nursing, which last year taught 80,000 women and girls, will be expanded in the next year to teach 500,000 American women in home nursing. This is now a new undertaking of the American Red Cross, Chairman Davis said, as more than 1,000,000 persons have received home nursing certificates since the home nursing program began in 1914. The course takes six weeks, covering twenty-four hours of class instruction, of which 70 per cent consists of practice work, making use only of such equipment as the average family would be expected to have. The care of babies, children and the aged and positive health measures are stressed. Under no circumstances, however, does the certificate presented for completion of the course entitle the receiver to serve outside her home for remuneration, nor is the instruction given intended to eliminate the need of professional or nursing assistance. The women receiving this home nursing instruction, Chairman Davis said, will be a vital adjunct to the overtaxed nursing, medical and hospital facilities and will be of great value to the nation in the event of epidemics or national defense emergencies.

ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

WAR DEPARTMENT

The following additional medical reserve officers have been ordered to extended active duty by the War Department, Washington, D. C.:

ABELE, John Frank, Captain, San Diego, Calif.
ATKINSON, Robert Henry, 1st Lieut., Walter Valley, Miss.
BAKER, John Samuel, 1st Lieut., Los Angeles.
BALLANTINE, Henry T., 1st Lieut., Chestnut Hill, Mass.
BARNHILL, John Robert, 1st Lieut., Bakersfield, Calif.
BERARD, Louis Nil, Captain, St. Louis.
BROWN, John Welch, 1st Lieut., San Francisco.
DURNIN, William George, 1st Lieut., Bottineau, N. D.
GRIFFIN, John Gordon, 1st Lieut., Rochester, Minn.
HARLEY, Robison D., 1st Lieut., Rochester, Minn.
HUNTINGTON, Camp Stanley, 1st Lieut., Washington, D. C.
LAMON, John Daniel, Jr., Captain, Albuquerque, N. M.
LOGUE, Robert Bruce, 1st Lieut., Atlanta, Ga.
MOODY, Leonard Wood, 1st Lieut., An-gwah-ching, Minn.
MORROW, Robert Prosser, Jr., 1st Lieut., New Orleans.
ODGERS, Stephen Lafayette, 1st Lieut., Chicago.
PASCUCCI, Lucien Michele, 1st Lieut., New York.
RECKLER, Sidney, Captain, Denver.
ROSS, Raleigh R., 1st Lieut., Lockhart, Texas.
SIMONSON, Eric Emil, 1st Lieut., Castlegate, Utah.
TENAGLIA, Eutimio Domenico, Major, Clayton, Mo.
WEBB, Robert W., 1st Lieut., Dallas, Texas.
WEXLER, Nathan Harold, Captain, Brooklyn.
WIENER, Morris Frederick, Captain, Brooklyn.
ZUCK, Frederick N., 1st Lieut., Rochester, N. Y.

Orders Revoked

FAZIO, Michael G., 1st Lieut., Brooklyn.
JOHNSON, Elgie K., 1st Lieut., Columbus, Ohio.
MARCH, Harry N., Captain, Grass Valley, Calif.
MILFORD, Albert F., Jr., 1st Lieut., Ypsilanti, Mich.
NEFF, Richard Scudder, 1st Lieut., Boston.
ROBERTS, Harold K., 1st Lieut., St. Louis.
WILKINSON, Thomas C., Captain, Pittsburgh.
WOLFF, Bruce N., 1st Lieut., Gettysburg, Pa.

FIRST CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, First Corps Area, which comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut:

CARIGNAN, Roland Z., 1st Lieut., Dover, N. H., Fort Devens, Mass.
DOUGHERTY, John F., 1st Lieut., Bath, Maine, Springfield, Mass.
DUSTON, Charles H., 1st Lieut., Westford, Mass., Camp Edwards, Mass.
GLENN, William W. L., 1st Lieut., Boston, Army Base, Boston.
HYMAN, Mayer H., 1st Lieut., Boston, Fort Devens, Mass.
JORDAN, Frank J., 1st Lieut., Stoughton, Mass., Army Base, Boston.
LARKIN, Donald F., 1st Lieut., Waterville, Maine, Fort H. G. Wright, N. Y.

Orders Revoked

ARCHAMBAULT, Henry A., 1st Lieut., Barre, Vt.
BELMONT, Ralph S., 1st Lieut., Sanford, Maine.
BERMAN, Leo, 1st Lieut., Boston.
BUERMANN, Henry, Jr., 1st Lieut., South Hero, Maine.
DORSEY, Joseph F., 1st Lieut., Boston.
DROBNES, Sidney, 1st Lieut., Norwich, Conn.
HALL, Walter L. H., 1st Lieut., Old Town, Maine.
HOPPER, Edward B., 1st Lieut., Glenbrook, Conn.
KRONICK, Macey, 1st Lieut., Greenfield, Mass.

SECOND CORPS AREA

The following additional medical reserve corps officers have been ordered to active duty by the Commanding General, Second Corps Area, which comprises the states of New York, New Jersey and Delaware:

BODIAN, Martin, 1st Lieut., Brooklyn, Fort Benning, Ga.
BODKIN, Edmund C., 1st Lieut., Bronx, N. Y., Fort Bragg, N. C.
BOUTON, Dale C., 1st Lieut., New York, Fort Bragg, N. C.
BRANNAN, Gordon Robert, 1st Lieut., Middletown, N. Y., Fort Benning, Ga.
BROGAN, Francis B., 1st Lieut., Paterson, N. J., Camp Blanding, Fla.
CASEY, Francis G., 1st Lieut., Brooklyn, Fort Hancock, N. J.
CHARTOCK, Hyman, 1st Lieut., Brooklyn, Fort Monmouth, N. J.
DeHOFF, John B., 1st Lieut., New York, Fort Monmouth, N. J.
DEMO, Robert A., 1st Lieut., Rochester, N. Y., Plattsburg Barracks, N. Y.
DOCTROW, William M., 1st Lieut., New York, Fort Bragg, N. C.
ESPINOZA, David V., 1st Lieut., Poughkeepsie, N. Y., Camp Davis, N. C.
FENTON, Alan Harold, 1st Lieut., Mount Vernon, N. Y., Fort Bragg, N. C.
FERNBACH, Paul A., 1st Lieut., Checktowaga, N. Y., Fort Bragg, N. C.
HARBESON, James P., III, 1st Lieut., West Collingswood, N. J., Fort Knox, Ky.
HARROW, Douglas G., 1st Lieut., New York, Camp Blanding, Fla.
JACOBS, Ralph, 1st Lieut., Brooklyn, Fort McClellan, Ala.
JANNARONE, Lewis H., 1st Lieut., Belleville, N. J., Fort Benning, Ga.
KLAIBER, John J., Jr., 1st Lieut., Buffalo, Plattsburg Barracks, N. Y.
LANZILLO, James L., 1st Lieut., Troy, N. Y., Camp Davis, N. C.
LICHTENBERG, Walter, 1st Lieut., New York, Fort Niagara, N. Y.
LIZZI, Arthur J., 1st Lieut., Brooklyn, Camp Davis, N. C.
LOVELOCK, Francis J., 1st Lieut., New York, Fort Niagara, N. Y.
LUSTBADER, Philip F., 1st Lieut., Brooklyn, Fort Tilden, N. Y.
MARCUS, Harold, 1st Lieut., Brooklyn, Camp Davis, N. C.
McFARLIN, Raymond Thomas, 1st Lieut., Bronx, N. Y., Fort Knox, Ky.
MENDONSA, Lawrence E., 1st Lieut., New York, Fort Jackson, S. C.
METZGER, William R., 1st Lieut., Bronx, N. Y., Fort Jackson, N. C.
ORFUSS, Abraham J., 1st Lieut., New York, Fort Dix, N. J.
PENNINGTON, Glenn W., 1st Lieut., New York, Fort Bragg, N. C.
PICKAR, Gabriel, 1st Lieut., Brooklyn, Fort Dix, N. J.
PLASSE, David H., Captain, New York, Fort Knox, Ky.
RICHARD, Donat R., 1st Lieut., Brooklyn, Fort Bragg, N. C.
ROGAN, Henry Aaron, Captain, Pleasantville, N. Y., Camp Davis, N. C.
ROMANO, Frank R., 1st Lieut., Bronx, N. Y., Camp Stewart, Ga.
ROSE, Anthony, 1st Lieut., Bronx, N. Y., Fort Bragg, N. C.
SCHNEIDER, Harry J., 1st Lieut., Long Branch, N. J., Camp Livingston, La.
SHIELDS, Charles D., Captain, Buffalo, Camp Croft, S. C.
SHIFF, Nathan A., 1st Lieut., Bronx, N. Y., Fort Bragg, N. C.
STERNBERGH, Waldemar C. A., 1st Lieut., Clifton Springs, N. Y., Fort Benning, Ga.
SULMONETTI, William B., 1st Lieut., Larchmont, N. Y., Fort Knox, Ky.
TRIPPE, Morton F., 1st Lieut., Asbury Park, N. J., General Dispensary, New York.
WHALEN, Edward P., 1st Lieut., Ogdensburg, N. Y., Fort Bragg, N. C.
YELLIN, Charles H., 1st Lieut., Roselle, N. J., Fort McClellan, Ala.
YESNER, Bernard, 1st Lieut., Richmond Hills, L. I., N. Y., Fort Bragg, N. C.

Orders Revoked

HERRINGTON, Lee R., Jr., 1st Lieut., Camp Shelby, Miss.
KASSAN, Robert Jacob, 1st Lieut., West Point, N. Y.
KUFLIK, William Eggert, 1st Lieut., Fort Knox, Ky.
SIMENSKY, Philip F., 1st Lieut., Air Base, Orlando, Fla.

THIRD CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Third Corps Area, which comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland:

ESTILL, Don Vincent, 1st Lieut., South Boston, Va., Camp Custer, Mich.
GRYNKEWICH, Serge Elias, 1st Lieut., Tamaqua, Pa., Camp Lee, Va.
HIMMELWRIGHT, Gabel G., 1st Lieut., Newport News, Va., Camp Lee, Va.
LEWIS, Paul Massillon, 1st Lieut., Pittsburgh. Aberdeen Proving Ground, Md.
LUKAS, Alexander Benjamin, 1st Lieut., Shenandoah, Pa., Indiantown Gap Military Reservation, Pa.
MOYER, Dwight Lester, 1st Lieut., Hatfield, Pa., Fort Story, Va.
MULHOLLAND, Richard Francis, 1st Lieut., Pittsburgh, Indiantown Gap Military Reservation, Pa.
POMEROY, James McCahan, 1st Lieut., Chester, Pa., Fort George G. Meade. Md.
POPIELARSKI, Joseph Thomas, 1st Lieut., Bridgeport, Pa., Aberdeen Proving Ground, Md.

POSTLETHWAIT, Raymond Woodrow, 1st Lieut., Palmerton, Pa., Fort Myer, Va.
REPPUN, John Iorwerth Frederick, 1st Lieut., Homestead, Pa., Fort Belvoir, Va.
ROUZER, Alvin Victor, 1st Lieut., Connellsville, Pa., Fort George G. Meade, Md.
SCANLAN, Thomas Joseph Daniel, 1st Lieut., Shillington, Pa., Camp Lee, Va.
SCHNALL, Charles, 1st Lieut., Philadelphia, Indiantown Gap Military Reservation, Pa.
SCULLY, John Pendleton, 1st Lieut., Pittsburgh, Indiantown Gap Military Reservation, Pa.
THOMPSON, William Taliaferro, Jr., 1st Lieut., Richmond, Va., Camp Lee, Va.
WALL, Norman Melvin, 1st Lieut., Girardville, Pa., Fort Eustis, Va.
WILSON, John Francis, 1st Lieut., West Philadelphia, Pa., Fort George G. Meade, Md.

Orders Revoked

HEIM, Hugh Wilson, 1st Lieut., Schuylkill Haven, Pa.
PROCOPIO, James Joseph, 1st Lieut., Shamokin, Pa.
STONE, Reuben Edwin, Captain, Glenn Dale Sanatorium, Glenn Dale, Md.

FOURTH CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Fourth Corps Area, which comprises the states of Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana:

BLOUNT, Robert Eames, 1st Lieut., Fort Lauderdale, Fla., Fort McClellan, Ala.
BURTON, John P., 1st Lieut., New Orleans, Fort Bragg, N. C.
CHAMBERS, Wallace L., Captain, Pickens, Miss., Camp Wheeler, Ga.
CLARK, James A., Jr., 1st Lieut., Ruleville, Miss., Fort Bragg, N. C.
DINAN, Joseph Francis, 1st Lieut., Carville, La., Camp Blanding, Fla.
GIDDENS, Isbin S., 1st Lieut., Millen, Ga., Camp Forrest, Tenn.
GRAVES, John Humphrey, 1st Lieut., Memphis, Tenn., Camp Forrest, Tenn.
GROOVER, Marshall E., 1st Lieut., Quitman, Ga., Camp Forrest, Tenn.
HAMMOND, Gaines W., 1st Lieut., Spartanburg, S. C., Camp Stewart, Ga.
HENRY, Hector Himel, 1st Lieut., Durham, N. C., Camp Shelby, Miss.
HUNTER, William B., Major, Lillington, N. C., Camp Shelby, Miss.
INGRAM, Aldean Starr, 1st Lieut., Griffin, Ga., Camp Shelby, Miss.
JOHANSEN, Frederick A., Major, Carville, La., Camp Livingston, La.
JOHNSON, John R., Major, Jackson, Miss., Camp Blanding, Fla.
McAFEE, John Colbert, 1st Lieut., Macon, Ga., Camp Blanding, Fla.
McKENZIE, Jack A., 1st Lieut., Miama, Fla., Camp Blanding, Fla.
SAMPOGNARO, Vincent J., 1st Lieut., Monroe, La., Camp Wheeler, Ga.
SAMSON, Martin F., 1st Lieut., New Orleans, Camp Stewart, Ga.
SMITH, Charles R., 1st Lieut., Dawson, Ga., Camp Livingston, La.
STANDER, Alvin A., 1st Lieut., Baton Rouge, La., Fort Bragg, N. C.
STOKES, Lowell L., 1st Lieut., Lake City, Fla., Fort Benning, Ga.
TERRELL, Kenneth D., 1st Lieut., Prentiss, Miss, Camp Blanding, Fla.
WADLINGTON, James E., 1st Lieut., Florence, Miss., Camp Shelby, Miss.
WHITFIELD, Frederick S., 1st Lieut., Columbia, La., Fort McClellan, Ala.
WOOD, James A., Lieut.-Colonel, Macon, Ga., New Orleans.
ZIEMAN, John Arthur, 1st Lieut., Mobile, Ala., Camp Davis, N. C.

Orders Revoked

ASKEW, Rufus A., 1st Lieut., Atlanta, Ga.
BURKHALTER, W. D., Captain, Memphis, Tenn.
GILL, Euclid Borland, 1st Lieut., New Orleans.
LOWRY, Harvey McL., 1st Lieut., Memphis, Tenn.
POOLE, William L., 1st Lieut., Fairfield, Ala.
SLIPAKOFF, Leon, 1st Lieut., New Iberia, La.
WILKES, John Burwell, 1st Lieut., Durant, Miss.
WILSON, John Mc., 1st Lieut., Memphis, Tenn.

SEVENTH CORPS AREA

The following additional medical reserve corps officers have been ordered to extended active duty by the Commanding General, Seventh Corps Area, which comprises the states of North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri, Arkansas and Wyoming:

AGNEW, James Ward, Captain, Iowa City, Fort Riley, Kan.
BAUER, Frank Louis, 1st Lieut., Shenandoah, Iowa, Corps Area Service Command Station Hospital, Camp J. T. Robinson, Ark.
CHAMBERS, James Quarles, Jr., Captain, Kansas City, Mo., Corps Area Service Command Station Hospital, Fort F. E. Warren, Wyo.
CHUNN, Stanley Sylvester, 1st Lieut., Pipestone, Minn., Corps Area Service Command Station Hospital, Fort Leavenworth, Kan.
CLARKE, Harry, Lieut. Col., Seward, Neb., Antiaircraft Training Center, Camp Hulen, Texas.
EPSTEIN, Joseph George, Captain, Wadsworth, Kan., Corps Area Service Command Induction Station, Jefferson Barracks, Mo.
FOOTE, Donovan Bryne, 1st Lieut., Hastings, Neb., Corps Area Service Command Station Hospital, Fort Crook, Neb.
FRACASSE, John, 1st Lieut., Des Moines, Iowa, Corps Area Service Command Station Hospital, Fort Des Moines, Iowa.
FREEDMAN, Albert Louis, 1st Lieut., Iowa City, Corps Area Service Command Station Hospital, Fort Leonard Wood, Mo.
GANSCHOW, John Henry, 1st Lieut., Hedrick, Iowa, Corps Area Service Command Station Hospital, Fort Leonard Wood, Mo.
GIER, Jacob Benjamin, 1st Lieut., Wadsworth, Kan., Corps Area Service Command Induction Station, Jefferson Barracks, Mo.
GINSBERG, William, Major, St. Paul, Antiaircraft Training Center, Camp Hulen, Texas.
GOLDEN, Robert Fred, Captain, Rochester, Minn., Corps Area Service Command Station Hospital, Camp J. T. Robinson, Ark.
HALL, Frank Wilburn, Captain, Cape Girardeau, Mo., Corps Area Service Command Station Hospital, Fort F. E. Warren, Wyo.
HANSON, Carl Alfred, 1st Lieut., Minneapolis, Corps Area Service Command Station Hospital, Fort Snelling, Minn.
HARRIS, Karl Sanders, 1st Lieut., Iowa City, Fort Riley, Kan.
HEDEMARK, Homer Harold, Captain, Thief River Falls, Minn., Fort Leonard Wood, Mo.
HOGE, Marlin Boyd, 1st Lieut., Fort Smith, Ark., Corps Area Service Command Station Hospital, Camp J. T. Robinson, Ark.
IDSTROM, Linneus Godfrey, 1st Lieut., Ah-gwah-ching, Minn., Fort Snelling, Minn.
KANTOR, Julius Max, 1st Lieut., Kansas City, Mo., Corps Area Service Command Station Hospital, Fort Leonard Wood, Mo.
KERSHNER, Calvin Myles, 1st Lieut., Brookings, S. D., Fort Snelling, Minn.
LONG, Fred Peyton, 1st Lieut., North Platte, Neb., Corps Area Service Command Station Hospital, Fort Riley, Kan.
NEVELN, Lowell Claus, 1st Lieut., Middle, Iowa, Corps Area Service Command Station Hospital, Fort Snelling, Minn.
PATTON, Bernard W., Captain, Des Moines, Iowa, Corps Area Service Command Induction Station, Camp J. T. Robinson, Ark.
PRESTON, Albert, Jr., 1st Lieut., Kansas City, Mo., Corps Area Service Command Station Hospital, Fort Riley, Kan.
RALSTON, Donald Everett, 1st Lieut., Minneapolis, Fort Snelling, Minn.
SCHUMAKE, Lawrence Powell, 1st Lieut., St. Louis, 4th Cavalry Brigade, Fort Riley, Kan.
SELINGER, Bernard, 1st Lieut., Red Lake, Minn., 368th Infantry, Fort Huachuca, Ariz.
SPRADLING, Richard Lee, 1st Lieut., Lincoln, Neb., Corps Area Service Station Hospital, Fort Omaha, Neb.
STROUGH, La Vern Craig, 1st Lieut., Beatrice, Neb., Corps Area Service Command Station Hospital, Fort Snelling, Minn.
THOMPSON, Carl Oliver, 1st Lieut., Hendricks, Minn., Corps Area Service Command Station Hospital, Fort F. E. Warren, Wyo.
WRAY, Robert Montimer, 1st Lieut., Cedar Rapids, Iowa, Fort Leonard Wood, Mo.
YELLEN, Benjamin Louis, 1st Lieut., Wadsworth, Kan., Corps Area Service Command Station Hospital, Fort Riley, Kan.
ZELIGS, Isadore, 1st Lieut., Iowa City, Corps Area Service Command Station Hospital, Fort Riley, Kan.

Orders Revoked

DWORKIN, Shiell, 1st Lieut., St. Louis.
MOORE, Ernest M., Jr., 1st Lieut., Higginsville, Mo.
NELSON, Nesmith P., Captain, Brainerd, Minn.
WATKINS, Lucien A., 1st Lieut., Leavenworth, Kan.

Relieved from Extended Active Duty

ANDERSON, Bruce Murat, 1st Lieut., Rochester, Minn., Corps Area Service Command Station Hospital, Camp J. T. Robinson, Ark.
BECHTOLD, Frederick Frank, 1st Lieut., St. Louis, Jefferson Barracks, Mo.
FEIST, George Van, Lieut-Colonel, Kansas City, Mo., Curtiss Wright Technical Institute, Glendale, Calif.
HALLADAY, George John, 1st Lieut., Brainerd, Minn., Camp J. T. Robinson, Ark.
HODGSON, Frank Harrison, 1st Lieut., Kansas City, Mo., Fort Leonard Wood, Mo.
KANE, Thomas Edward, 1st Lieut., Boone, Iowa, Corps Area Service Command Station Hospital, Fort Leonard Wood, Mo.

ORGANIZATION SECTION

OFFICIAL NOTES

EXHIBITS FROM HEADQUARTERS

November 1-30.—Phoenix, Ariz. (for use throughout the state by the Committee on Public Health Education of the Arizona State Medical Association:

Question and answer exhibit.

November 3-7.—American College of Surgeons, Boston (annual meeting):

Information About Hospitals.

November 10-13.—Southern Medical Association, St. Louis (annual meeting):

Nutritionally Improved Flour.

November 17-30.—Cleveland Health Museum, Cleveland:

Nutritionally Improved Flour.

November 21-22.—Pacific Coast Section of the American Student Health Association, San Francisco:

Use and Abuse of the Barbiturates.
Chemistry of the Sulfonamides.

ADDRESSES BY THE PRESIDENT

Dr. Frank H. Lahey, President of the American Medical Association, has been scheduled to deliver the following addresses during November:

November 7.—American College of Surgeons, Boston.
November 10-11.—Southern Medical Association, St. Louis.
November 18.—Medical Society of Post of Camp Devens, Ayer, Mass.
November 25.—Berkshire County District Medical Society, Pittsfield, Mass.

WOMAN'S AUXILIARY

Georgia

Mrs. J. M. Barnett, Albany, Ga., one of the charter members and past president of the Dougherty County auxiliary, was recently selected as Dougherty County's outstanding woman citizen. Mrs. Barnett is active in many other community and national woman's organizations.

Mrs. W. E. Simmons, Metter, at a recent meeting in Savannah, was elected president of the Woman's Auxiliary to the First District Medical Society. The speakers at this meeting were Dr. Robert V. Schultz, of the state department of health; Dr. Allen H. Bunce, Atlanta, president of the Medical Association of Georgia, and Dr. James N. Brawner, Atlanta.

New Jersey

The Woman's Auxiliary to the Camden County Medical Society met, May 1, with Mrs. Lawrence L. Glover presiding. Eighty-two persons were present and three guests of honor—Mrs. R. J. McDonald, state auxiliary president; Mrs. James Hunter, former state president, and Mrs. William Raleigh, former Camden County president. Mrs. Oswald R. Carlander, recently elected state auxiliary president, who is also president of the New Jersey Division of the American Association of University Women, asked for continued cooperation of the auxiliary members. Mrs. L. R. Wilson, treasurer, reported that $378.40 was realized from the Fashion Show and Card Party. Donations given to several Camden County organizations amounted to $317.

Pennsylvania

Dr. Edward L. Bortz, president of the Philadelphia County Medical Society, Philadelphia, was the speaker at the health education day of the Berks County auxiliary recently. He discussed diabetes and showed colored motion pictures of Camp Firefly, a camp for diabetic children sponsored by the John B. Deaver Auxiliary of the Lankenau Hospital. This beautiful camp is along the Perkiomen Creek, and its activities, which are directed by Dr. Bortz, range from teaching children to weigh their own food and to administer their own insulin to teaching them carefully supervised outdoor sports and handicrafts.

Texas

The twenty-third annual session of the Woman's Auxiliary to the State Medical Association of Texas was held in Fort Worth, May 12-15, 1941 with a registration of four hundred and forty-five. A dinner honoring Mrs. William Hibbitts, members of the state executive board, past presidents of the state auxiliary, county presidents, nominating committee and their husbands was held at the Blackstone Hotel. The local chairman of arrangements was Mrs. A. B. Pumphrey, assisted by Mrs. W. Frank Armstrong and Mrs. J. R. Wise.

On Wednesday, the business meeting of the auxiliary was held at the Blackstone, with Mrs. William Hibbitts presiding. Mrs. W. R. Thompson installed the new officers, following which Mrs. Hibbitts handed the gavel over to Mrs. S. F. Harrington, Dallas, the incoming president.

Falls County auxiliary entertained members of the Falls County Medical Society, May 6, with a picnic supper and fish fry at the Marlin Country Club.

The following officers of the Hidalgo County auxiliary were elected at the May meeting: president, Mrs. D. C. Hyder, Donna; vice president, Mrs. H. E. Whigham, McAllen; second vice president, Mrs. L. H. Moore, McAllen; secretary-treasurer, Mrs. M. R. Lawler, Mercedes. Mrs. G. A. Guerra gave a talk on dysentery. Mrs. Emma McCrary reviewed Hergescheimer's book "Java Head."

The auxiliary to the medical society of Liberty and Chambers counties entertained with a tea recently at the home of Mrs. E. R. Richter, Dayton. June 12 it met at the home of Mrs. Frank S. Griffin Jr. of Liberty. The auxiliary won the silver cup for the largest increase in membership of any county auxiliary; won third place in exhibits at the state auxiliary meeting and was one of eleven county auxiliaries that reported 100 per cent of its membership readers of THE JOURNAL. The following officers were installed: Mrs. Jack Bevil, president; Mrs. A. R. Shearer, vice president; Mrs. R. C. Bellamy, secretary-treasurer, and Mrs. W. H. Bridges, parliamentarian.

Washington County auxiliary entertained two hundred women with a reception at Brenham, May 26. Mrs. Robert A. Hasskarl, president of the district auxiliary, and Mrs. N. D. Jarrell, incoming president of the county auxiliary, presided at the tea table. Other members of the auxiliary assisted in serving refreshments. Musical selections were given by Mesdames Jerry Hicks, Wayne Alexander, H. L. Steinbach and Kate E. McAdam. Mrs. C. E. Southern, Burton, retiring president, installed the following new officers: Mrs. N. D. Jarrell, president; Mrs. W. F. Hasskarl, vice president; Mrs. Fred Graber, recording secretary; Mrs. E. V. Pazdral, corresponding secretary; Mrs. George Zeiss, treasurer; Mrs. C. E. Southern, parliamentarian; Mrs. N. L. Schiller, press reporter, and Mrs. Arthur Becker, historian.

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

ARKANSAS

District Meetings.—The First Councilor District Medical Society was addressed in Jonesboro, October 15, among others, by Dr. Ralph M. Stuck, Denver, on "Care of the Simple Head Injury."——The speakers before the Second District Medical Society in Batesville, October 13, included Drs. William Decker Smith, Texarkana, on "Surgery of the Colon"; Merlin J. Kilbury, Little Rock, "Fungous Infections," and Francis Walter Carruthers, Little Rock, "Surgery of the Knee." Dr. Herbert Fay H. Jones, Little Rock, president of the state medical society, also spoke.——The Fifth Councilor District Medical Society was addressed in Camden, October 9, by Drs. Elliott Mendenhall and Robert R. Shaw, Dallas, Texas, on diseases of the chest. Hon. John L. McClellan, Camden, gave a talk entitled "Our American Heritage."

CONNECTICUT

Changes in Health Officers.—Dr. Roy V. Sanderson has been appointed health officer of Winsted to succeed Dr. Francis Gallo. Dr. Gilbert E. Moore is the acting health officer of Darien to fill the vacancy caused by the death of Dr. William H. Slaughter. Dr. Alfred Schiavetti, Stafford Springs, has been named acting health officer of West Willington during the absence of Dr. Frank B. Converse.

GEORGIA

New Home of Fulton County Medical Society.—The new Academy of Medicine of the Fulton County Medical Society, Atlanta, now under construction, will be dedicated on December 15. Dr. Fred W. Rankin, Lexington, Ky., President-Elect of the American Medical Association, will be the guest speaker. The new building supplants the old academy, which was located at 38 Prescott Street, N. E., purchased by the society in 1922. Excavation began June 10. The building is of Greek revival architecture and the exterior finish is of

Academy of Medicine in Atlanta.

stucco on brick. It is fireproof and air conditioned. The cost of the building and lot will be $140,000, most of which was raised by donations from the members. The building will contain the offices of the society, the offices of the Medical Association of Georgia, medical library and an auditorium with a seating capacity of 300, together with auxiliary headquarters, lounge rooms, recreation rooms, kitchen and dining room. Features of the decorative plans of the building include the installation of memorials to past presidents and members of the Fulton County Medical Society who have been active in its development.

ILLINOIS

Society News.—Dr. Charles S. White, Washington, D. C., discussed "Use of Blood Plasma in Surgery" before the Peoria Medical Society on October 14.—The Sangamon County Medical Society was addressed in Springfield, October 2, by the following Decatur physicians: Clarence E. Bell, "Observations on Dehydration Therapy"; Scott J. Wilkinson, "Clinical Study of Respiratory Infections in Children," and Dean F. Stanley, "Complications of Coronary Thrombosis."—Dr. James L. Mudd, St. Louis, addressed the Adams County Medical Society in Quincy, October 13, on "Empyema: Its Diagnosis and Treatment."

Tri-County Meeting.—The medical societies of Knox, Warren and Henry counties will meet in Galesburg, November 13, to hear the following Chicago physicians:

Dr. Howard L. Alt, The Common Blood Diseases Seen in General Practice.
Dr. Ralph A. Reis, Office Gynecology.
Dr. Francis L. Lederer, Clinical Significance of Hoarseness (motion pictures in kodachrome of the various laryngeal conditions causing hoarseness).
Dr. Geza de Takats, Peripheral Vascular Disease.

Southern Illinois Medical Association.—The sixty-seventh annual meeting of the Southern Illinois Medical Association will be held in Murphysboro, November 6. The program has been designed to interest the general practitioner. The speakers will be:

Dr. Frank M. Keiser, Murphysboro, Spinal Anesthesia.
Dr. Willard C. Scrivner, East St. Louis, Importance of Prenatal Care.
Dr. Gilbert H. Edwards, Pinckneyville, Postpartum Care of Mother Including Early Care of Infant.
Dr. Andy Hall Jr., St. Louis, Urologic Problems of the General Practitioner.
Dr. Frederick V. Emmert, St. Louis, Management of Difficult Labor by the General Practitioner.
Dr. Ralph A. Kinsella, St. Louis, Medical Management of Nephritis.
Mr. Josiah Whitnel, attorney at law, East St. Louis, Medicolegal Problems of the General Practitioner.
Dr. James J. Donahue, East St. Louis, Pediatrics in General Practice.
Dr. Everett P. Coleman, Canton, Diagnosis of Obscure Abdominal Conditions.
Dr. James H. Hutton, Chicago, Endocrine Therapy Including That of the Menopause.
Dr. Frederick A. Jostes, St. Louis, Low Back Pain.
Dr. Carl G. Morlock, Rochester, Minn., Problem of the Small Ulcerating Gastric Lesion.
Dr. Roy H. Milligan, St. Louis, Acute Otitis Media.
Dr. Charles H. Phifer, Chicago, Vascular Accidents in Abdominal Surgery.

At the banquet the speakers will include Drs. Charles O. Lane, West Frankfort, president of the Southern Illinois Medical Association; James S. Templeton, Pinckneyville, past president of the state society, and Andy Hall, Mount Vernon.

Chicago

Dr. Koch Made Professor Emeritus.—Fred C. Koch, Ph.D., Frank P. Hixon distinguished service professor and chairman of the department of biochemistry of the University of Chicago, retired October 1 with the title emeritus, having reached the retirement age of 65. Dr. Koch received his Ph.D. degree at Chicago in 1912 and in the same year became instructor of physiologic chemistry there. He subsequently served as associate professor, professor of biochemistry and chairman of the department. He is an Associate Fellow of the American Medical Association and a member of the Institute of Medicine of Chicago and in 1937 was president of the Association for the Study of Internal Secretions. In 1926 he was secretary of the Society of Biological Chemists. Dr. Koch's research has dealt largely with study of hormones.

Society News.—Drs. Virgil P. W. Sydenstricker, Augusta, Ga., and Walter E. Dandy, Baltimore, discussed "Vitamin Deficiencies" and "Diagnosis and Treatment of Lesions of the Cranium," respectively, before the North Side Branch of the Chicago Medical Society, October 16.——The Chicago Gynecological Society was addressed, October 17, by Drs. James H. Beaton, Grand Rapids, Mich., and David S. Hillis on "Influence of an Antispasmodic Drug upon the Cervix in Labor" and Solomon J. Benensohn, "Pregnancy in Syphilitic Mothers at the Cook County Hospital (935 Pregnancies)."——At a meeting of the Robert Sonnenschein Study Group for Medical History in Michael Reese Hospital, October 15, Drs. Frederick Stenn spoke on "Milk Sickness"; Herbert Rattner, "Historical Aspects of Baldness," and Benjamin B. Beeson, "Georges Clemenceau the Physician."

IOWA

Postgraduate Programs.—In the series of postgraduate programs conducted by the Polk County Medical Society, Des Moines, Dr. William P. Murphy, Boston, will speak, November 12, on "The Treatment of Anemia." Members of the society will present this program on December 17:

Dr. Richard F. Birge, Newer Laboratory Methods.
Dr. Lee F. Hill, Idiopathic Hypoparathyroid Tetany—Calcium Metabolism.
Dr. John Russell, The Tuberculosis Problem.
Dr. Frank W. Fordyce, Surgical Treatment of Pulmonary Tuberculosis.

KENTUCKY

Changes in Health Officers.—Dr. James H. Wells, Hickman, health officer of Fulton and Hickman counties, has been appointed health officer of Bell County to succeed Dr. Adam Stacy Jr., Pineville, who resigned to enter private practice. Dr. Layson B. Swann, Clinton, has been appointed head of the Fulton-Hickman counties unit.

Society News.—Drs. Joseph Andrew Bowen and Jacob S. Bumgardner, Louisville, addressed the Jefferson County Medical Society, Louisville, October 20, on "Urology in Infancy and Childhood" and "Common Lesions of the Larynx" respectively.——Drs. James W. Bruce and Morris Flexner, Louisville, addressed the Bourbon County Medical Society, Paris, September 25, on "Acute Rheumatic Fever."——Dr. Chauncey W. Dowden, Louisville, addressed the Louisville Medico-Chirurgical Society, October 24, on "An Evaluation of the Present Knowledge of Vitamin B."

MICHIGAN

Sixteenth Annual Clinic.—The Highland Park Physicians' Club held its sixteenth annual clinic on October 29. Mayor Blaine T. Colman opened the program with an address of welcome. Dr. Plinn F. Morse, Detroit, was chairman of a round table discussion on "Postoperative Complications," which was participated in by Drs. Geza de Takats, Chicago; Reed M. Nesbit, Ann Arbor; Ivan B. Taylor, Detroit; Arthur E. Hammond, Detroit, and Fredrick F. Yonkman, Detroit. In the afternoon the program was presented by the following:

Dr. de Takats, Vascular Emergencies of the Extremities.
Dr. Frederick H. Falls, Chicago, The Falls Test and Various Other Tests for Pregnancy.
Dr. John A. Toomey, Cleveland, Infantile Paralysis.
Dr. Carl E. Badgley, Ann Arbor, Immediate Treatment of the Common Fractures.

Dr. Vaughan Named Dean of Public Health School.—Henry F. Vaughan, Dr.P.H., professor of public health at the University of Michigan Medical School, Ann Arbor, has been appointed dean of the new School of Public Health at the university and chairman of the department of public health practice. Under the new setup, Drs. Thomas Francis Jr. and Lowell T. Coggeshall of the Rockefeller Foundation, New York, will be professor and chairman of the department of epidemiology and professor of epidemiology, respectively. Dr. John Sundwall, former professor and director of the division of hygiene and public health, has been named professor of hygiene and public health. Other transfers into the new unit include:

Nathan Sinai, Dr.P.H., professor of public health.
Dr. Emory W. Sink, assistant professor of public health.
Kenneth A. Easlick, D.D.S., assistant professor of public health dentistry.
Marguerite F. Hall, Ph.D., assistant professor of biometrics.
Lloyd R. Gates, Dr.P.H., instructor in public health engineering.
Dr. Lavinia G. MacKaye, instructor in child health.
Dr. David A. VanderSlice, instructor in school health.

The new School of Public Health has been made possible by two gifts of $500,000 each by the W. K. Kellogg Foundation and the Rockefeller Foundation. Half the total will be applied to the cost of the site, building and equipment and the other half to maintenance over a ten year period.

MINNESOTA

Mayo Lectures on Civilian and Military Practice.—The Mayo Foundation for Medical Education and Research, Rochester, announces that a series of lectures, demonstrations and clinics by members of the faculty and invited guests will be held during the week of November 10. Problems related to medical and surgical emergencies encountered in civilian and military practice will be emphasized. Physicians are invited to attend.

Society News.—Dr. Warfield M. Firor, Baltimore, discussed "Tetanus: Experimental and Clinical Study" in a Mayo Foundation lecture at the Mayo Clinic, Rochester, October 9. Ernest O. Lawrence, Ph.D., professor of physics, University of California, Berkeley, delivered a Mayo Foundation lecture October 8 on "Artificial Radio-Activity and the Cyclotron in Medicine."——Dr. Maurice B. Visscher, Minneapolis, considered "Problems in Aviation Medicine" in his thesis before the Minnesota Academy of Medicine, St. Paul, October 8.——Dr. Charles E. Connor, St. Paul, discussed "Present Status of the Surgery of the Nasal Accessory Sinuses" before the Ramsey County Medical Society in St. Paul, September 29, and Dr. John J. Hochfilzer, St. Paul, "Nasal Sinuses as Foci of Infection."

MISSOURI

Lecture on Cancer Research.—Dr. James B. Murphy, New York, will deliver the third Barnard Hospital Lecture, sponsored by the Barnard Free Skin and Cancer Hospital, St. Louis, before the St. Louis Medical Society, St. Louis, November 18. His subject will be "An Analysis of the Trends in Cancer Research."

NEW YORK

Lectures for Sullivan County Society.—The council committee on public health and education of the Medical Society of the State of New York arranged the following series of lectures for the Sullivan County Medical Society:

Dr. Paul W. Beaven, Rochester, Deficiency Diseases of Children, October 15, in Monticello.
Dr. Marjorie F. Murray, Cooperstown, Physical Examination of Children, October 22, in Liberty.
Dr. Charles Hendee Smith, New York, Diet in Infancy and Childhood, October 29, in Woodbourne.
Dr. Albert D. Kaiser, Rochester, Rheumatic Fever and Heart Disease, November 5, in Liberty.
Dr. Francis J. Carr Jr., New Rochelle, Poliomyelitis—Practical Suggestions in the Treatment and Care of a Poliomyelitis Case, November 12, in Monticello.
Dr. Carr, The New York State Program for the Rehabilitation of Handicapped Children, November 19, in Liberty.
Dr. Abraham Clement Silverman, Syracuse, Infectious Diseases of Childhood, November 26, in Liberty.

Tuberculosis Case-Finding Study.—The South Brooklyn Medical Society, in cooperation with the Medical Society of the County of Kings, the Academy of Medicine of Brooklyn and the Brooklyn Tuberculosis and Health Association, on December 1 will begin a case-finding study for tuberculosis among the patients of private physicians practicing in the Red Hook-Gowanus Health District. The survey will run for a six months' period. A general meeting will be held November 6 to discuss "The Medical Profession's Job as Viewed by the Health Department," "Diagnosis Measures Which the Medical Profession Can Employ," "Differential Diagnosis of Pulmonary Tuberculosis from Other Forms of Chest Pathology" and "A Challenge to the Medical Profession." A four day course on tuberculosis, open to all physicians cooperating in the survey, will be held at the Red Hook-Gowanus Health Center, November 12-19.

Postgraduate Institute at Rochester.—The University of Rochester School of Medicine and Dentistry and the Medical Society of the County of Monroe, in cooperation with the Medical Society of the State of New York, will conduct a postgraduate institute in Rochester November 11-13. The institute takes the place this year of the annual postgraduate course of the Monroe County Medical Society and the annual postgraduate conference of the state medical society. The program will include a forum on "Laboratory Methods in Clinical Medicine," conducted by Dr. Russell L. Haden, Cleveland. Dr. Howard W. Haggard, New Haven, Conn., will address a special session of the county medical society the first evening on "Johannes Müller and the Modern Conception of Cancer." The second evening Dr. John A. Toomey, Cleveland, will present the Monroe County Medical Society Lecture on "Poliomyelitis." The Eastman Memorial Lecture will be delivered Thursday evening by Dr. Edward William Alton Ochsner, New Orleans, on "Treatment of Intravenous Clotting." Participants in a question box period Wednesday afternoon will be Drs. John Murray Steele and Hugh Auchincloss, both of New York, and Dr. Ochsner and Dr. Toomey. The program also includes discussions on endocrine disorders, infectious diseases, problems in the treatment of adult tuberculosis, peripheral arterial disease and a symposium on the newborn period, offered by the American Academy of Pediatrics in cooperation with the Rochester Pediatric Society.

New York City

Clinic to Help Voiceless Patients.—The National Hospital for Speech Disorders, 61 Irving Place, has opened a clinic to rehabilitate patients who have become voiceless through loss of the larynx. Treatment aims to develop a substitute voice, and at the same time social aid is given the patient to help him become readjusted to his surroundings.

Dr. Whipple Awarded Bigelow Medal.—Dr. Allen O. Whipple, Valentine Mott professor of surgery, Columbia University College of Physicians and Surgeons, will be presented with the Bigelow Medal by Dr. David Cheever, Boston, on behalf of the Boston Surgical Society at a special meeting in Boston, November 7, for his contributions to the advancement of surgery. Dr. Irving J. Walker, president of the society, will introduce Dr. Whipple, whose address will be entitled "Present Day Surgery of the Pancreas."

Society News.—At a meeting of the New York Society for Clinical Ophthalmology, October 6, the speakers were Drs. George I. Swetlow, Brooklyn, on "The Physician in Court"; Morris Davidson, "The Ophthalmologist as an Expert Witness in Compensation Cases," and Percy Fridenberg, "Some Medicolegal Aspects of Ophthalmology."——Drs. Frederick H. Amendola and Harold Neuhof addressed the New York Surgical Society, October 8, on "Repair of Hernia with Silk-Binding Stitch" and "An Operative Procedure for Inguinal

Hernia Based on Buttressing the Undefended Space" respectively.——Dr. William P. Murphy, Boston, addressed the Medical Society of the County of Kings, October 21, on "Chronic Leukemia" and "Esophageal Hiatus Hernia (an unpublished paper)."

Public Lectures.—The Brooklyn Institute of Arts and Sciences, the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn are cooperating in a series of "Lectures to the Laity." The series opened October 28 with Dr. Howard W. Haggard, director of the laboratory of applied physiology, Yale University, New Haven, discussing "Devils, Drugs and Doctors." Other lecturers will be:

Dr. Thomas A. Gonzales, chief medical examiner, Relation of Medicine to Crime Detection, November 25.
Dr. Foster Kennedy, professor of clinical medicine (neurology), Cornell University Medical College, What and Why Is Your Mind, January 27.
Dr. George Draper, associate professor of clinical medicine, Columbia University College of Physicians and Surgeons, The Man Within the Patient, February 24.
Dr. Walter C. Alvarez, senior consultant in medicine, Mayo Clinic, Rochester, Minn., Food, Faith and Civilization, March 24.

OHIO

Medical Institute in Toledo.—Round table discussion by members of the staff of the department of physiology of Cornell University Medical College, New York, made up the program of the Medical Institute of the University of Toledo in the university's auditorium, Toledo, October 31. The speakers were Drs. McKeen Cattell, associate professor of pharmacology, Eugene F. Du Bois, professor of physiology, and Harry Gold, assistant professor of pharmacology. Topics discussed include "Digitalis: New Light on an Old Drug," "Management of Heart Failure" and "Circulatory Stimulants and Shock."

Personal.—Dr. Hans P. Lee, assistant physician at the Toledo State Hospital for twelve years, has been named superintendent of the Cleveland State Hospital.——Dr. Mortimer Herzberg was recently guest of honor at a dinner given by members of the staff of Jewish Hospital, Cincinnati, to mark his retirement as head of the clinical laboratory after eighteen years' service.——Dr. Mary A. Graber, Columbus, has been appointed chairman of the Franklin County Council on Nutrition for National Defense.——Dr. Donald D. Shira, for four years assistant secretary and medical adviser of the Ohio Public Health Association and associate editor of *Ohio Public Health*, has resigned to return to private practice in La Rue. He will continue as medical editor of *Ohio Public Health*.——Major Claude S. Perry, Medical Reserve Corps, U. S. Army, Columbus, has been designated as state reemployment officer in charge of directing efforts of local draft boards in obtaining employment for draftees who have been released from military service. He will continue with his work as assistant chief medical officer of Selective Service for Ohio.——Dr. John A. Carter, Batavia, health officer of Clermont County since 1936, has been appointed health officer of Middletown to succeed the late Dr. George D. Lummis.——Three psychiatrists were recently appointed to the Cleveland-Cuyahoga County psychiatric clinic; they are Drs. Arthur A. Roth, Cleveland Heights; Wilfred M. Gill, Lakewood, and Harry A. Lipson, Cleveland Heights.

PENNSYLVANIA

Society News.—Dr. Emil Novak, Baltimore, addressed the Cambria County Medical Society, Johnstown, October 9, on "Clinical Use of the Female Sex Hormone."——Dr. Joseph H. Barach, Pittsburgh, discussed "Diabetes as a Scientifically Treated Disease" before the Crawford County Medical Society at Meadville, October 15.——The Lackawanna County Medical Society was addressed in Scranton, October 28, by Dr. John L. Kantor, New York, on "Affections of the Small Intestine and Colon as Seen by the General Practitioner."——Harold Westlake, Ph.D., discussed "Cause and Treatment of Speech Defects" before the Centre County Medical Society in Bellefonte, October 16. Dr. Westlake is supervisor of speech correction in the Pennsylvania State Department of Public Instruction, Harrisburg.

Philadelphia

Society Studies Health of Its Members.—The Philadelphia County Medical Society has announced the establishment of a committee for the preservation of the health of physicians to make a five year study of the physical and mental history of 1,000 local physicians, newspapers report. The group to be studied will be taken from the membership of the society.

Society News.—Dr. Francis C. Grant delivered the annual oration of the Philadelphia Academy of Surgery, October 13, on "Brain Abscess."——Dr. Hans G. Schlumberger, among others, addressed the Pathological Society of Philadelphia, October 9, on "Rudolf Virchow—Revolutionist."——The Philadelphia Neurological Society was addressed by Drs. Joseph Stokes Jr. and Pascal F. Lucchesi,, October 24, on the epidemiology of poliomyelitis and "Character of the Poliomyelitis of 1940-1941," respectively.

WASHINGTON

State Medical Election.—Dr. Albert P. Duryee, Everett, was named president-elect of the Washington State Medical Society at its recent annual meeting in Seattle and Dr. George W. Cornett, Yakima, was installed as president. Dr. Herbert E. Coe, Seattle, is vice president of the society. The annual meeting for 1942 will be held in Spokane.

Survey of Poliomyelitis.—The George Williams Hooper Foundation of the University of California Medical School, San Francisco, recently conducted a survey of poliomyelitis and encephalitis in Yakima and surrounding territory, under the supervision of Dr. William D. Hammon. The viruses of St. Louis encephalitis and western equine encephalomyelitis were isolated from mosquitoes and by neutralization tests of more than 400 mammals and birds; extensive domestic reservoirs were found, according to a report from the university. Several members of the staff of the foundation working on the survey returned to the university September 17.

GENERAL

Sedgwick Medal Awarded to Dr. Armstrong.—The American Public Health Association at its recent annual meeting in Atlantic City, N. J., awarded the gold Sedgwick Memorial Medal "for distinguished service in public health" to Dr. Charles Armstrong, senior surgeon, U. S. Public Health Service, and investigator at the National Institute of Health, Bethesda, Md. Dr. Armstrong graduated at Johns Hopkins University School of Medicine, Baltimore, in 1915, joining the public health service the following year. Dr. Armstrong is credited with basic work in research of the transmission of sleeping sickness, psittacosis and infantile paralysis.

Changes in Status of Licensure.—The District of Columbia Commission on Licensure reports the following:

Dr. George J. Allen, Washington, license revoked, June 6, for his conviction of violation of the Harrison Narcotic Act.

The Minnesota State Board of Medical Examiners reports the following:

Dr. Harry A. Miller, Fairmont, license suspended for three years, July 11, having been found guilty of performing an abortion.

The Vermont State Board of Registration in Medicine announces the following:

Dr. Maximilian L. Herzig, New York, license revoked, June 17, because of lack of satisfactory evidence that he had completed a four year resident medical course in an approved medical school, as required under the Vermont Medical Practice Act. The Vermont license was granted on endorsement of Nevada credentials.

Central Society for Clinical Research.—The fourteenth annual meeting of the Central Society for Clinical Research will be held at the Drake Hotel, Chicago, November 7-8, under the presidency of Dr. Lawrence D. Thompson, St. Louis. Included among the speakers will be:

Dr. Josef Warkany and Rose Nelson, Ph.D., Cincinnati, Ohio, Congenital Malformations on a Nutritional Basis in Rats.
Dr. Edgar S. Gordon, Madison, Wis., The Therapeutic Use of a Synthetic Estrogen.
Drs. Arthur W. Frisch and Alvin E. Price, Detroit, Sputum Studies in Pneumonia: The Selection of Therapy.
Drs. William C. Buchbinder and Frank Neuwelt, Chicago, The Localization of Human Bundle Branch Block.
Dr. Elmer L. Sevringhaus, Madison, Wis., Treatment of Parathyroid Tetany.
Dr. William C. Beck, Chicago, Studies of the Appendiceal Fecalith.
Dr. George E. Wakerlin, Clarence A. Johnson, Ph.D., Dr. Bernard Gomberg, Edwin L. Smith, M.S., and George A. Olander Jr., Chicago, Treatment of Experimental Renal Hypertension with Renin.
Dr. Nathan S. Davis III, Chicago, Chronic Sub-Nutrition and Essential Hypertension.

College of Surgeons Meeting.—The thirty-first annual Clinical Congress of the American College of Surgeons will be held at the Statler and Copley-Plaza hotels, Boston, November 3-7. Dr. Evarts A. Graham, St. Louis, will deliver his address as retiring president Monday evening on "American Surgery in a Changing World," and Dr. William Edward Gallie, Toronto, the incoming president, will present the annual oration on surgery Tuesday evening on "Lessons Learned in the Great War." Dr. Walter Estell Lee, Philadelphia, will give the oration on fractures and other traumas Wednesday evening. A new feature this year will be a "Forum on Fundamental Surgical Problems," formulated by a committee under the chairmanship of Dr. Owen H. Wangensteen, Minneapolis,

and designed for younger men, representing various university departments, to present important results of their clinical and experimental research. The general program includes symposiums, panel discussions, clinics and clinical pathologic conferences.

Grant for Study of Private Health Agencies.—A three year comprehensive study of the activities of all private health agencies is to be undertaken by the National Health Council, under a special grant of $75,000 from the Rockefeller Foundation. The report of the survey will attempt to answer such broad questions as What are the various types of state and local voluntary health agencies? What fields do they cover? What methods of cooperation with official health agencies have they established? What do they cost to operate? What types of health work lead to the greatest active participation on the part of the citizens? Selskar M. Gunn, C.P.H., vice president of the Rockefeller Foundation, will direct the study at the request of the National Health Council, which was established by the foundation in 1921. Mr. Gunn returned to America recently after a long stay abroad as director of the European headquarters of the Rockefeller Foundation in Paris, now closed because of the war. Previously he had been in charge of the foundation's program of rural reconstruction in China.

Conference on Industrial Health.—The second American Conference on Industrial Health will be held at the Chicago Towers Club, Chicago, November 5-6. Sessions will be devoted to the technical problems of industrial health, the economics of industrial health, the social implications of industrial health and defense activities and industrial health. One luncheon meeting will cover "Health Service in Small Groups"; the second, "The Problem of Women in Industry." The dinner session will consider "Industrial Health, Defense and the Private Practitioner." Speakers at the various sessions will include:

Dr. Morris Fishbein, Editor of THE JOURNAL, Chicago.
Mr. Harold F. North, head of the industrial relations department of Swift & Company, Chicago.
Mr. Terence F. Cunneen, executive assistant for insurance, U. S. Chamber of Commerce, Washington, D. C.
Mr. Verne Zimmer, director, division of labor standards, U. S. Department of Labor, Washington, D. C.
Dr. Fred J. Wampler, professor of preventive medicine, Medical College of Virginia, Richmond.
Mr. F. A. Virkus, president of the Illinois Division of National Small Business Men's Association, Chicago.
Col. Donald Armstrong, executive officer, Ordnance Department, U. S. Army, Chicago.
Dr. Walter Clarke, executive director, the American Social Hygiene Association, New York.

The American Conference on Industrial Health aims to raise the standards of health for the employed population. The American Conference on Industrial Health was incorporated, not for profit, under the laws of Illinois in 1940.

Interns from Latin America.—Thirty-seven interns representing fifteen nations of South, Central and Caribbean America recently arrived in the United States to spend a year in United States hospitals and medical schools. The interns have received fellowships for study in this country through the cooperation of the Office of the Coordinator of Inter-American Affairs, the Pan American Sanitary Bureau and the participating institutions. The committee of sponsors for the plan under which these interns are studying is composed of the following:

Drs. Walter W. Palmer, Bard professor of medicine; Allen O. Whipple, Valentine Mott professor of surgery, Rustin McIntosh, professor of pediatrics, Columbia University College of Physicians and Surgeons, New York.
Dr. William S. Ladd, dean and professor of clinical medicine, Cornell University Medical College, New York.
Dr. Currier McEwen, dean and associate professor of medicine, New York University College of Medicine, New York.
Dr. William S. McCann, Charles A. Dewey professor of medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.
Dr. Oswald H. Robertson, professor of medicine, University of Chicago School of Medicine.
Dr. L. Whittington Gorham, professor of medicine and director of the department, Albany Medical College, Albany, N. Y.
Dr. William J. Kerr, professor of medicine, University of California Medical School, San Francisco.
Dr. Francis G. Blake, dean, Yale University School of Medicine, New Haven, Conn.
Dr. William D. Cutter, Secretary, Council on Medical Education and Hospitals, American Medical Association, Chicago.
Dr. Marion A. Blankenhorn, Gordon and Helen Hughes Taylor professor of medicine, University of Cincinnati College of Medicine.
Dr. Herman G. Weiskotten, dean, Syracuse University College of Medicine, Syracuse, N. Y.
Dr. George M. Mackenzie, chief of staff of the Mary Imogene Bassett Hospital, Cooperstown, N. Y.

Southern Medical Association.—The thirty-fifth annual meeting of the Southern Medical Association will be held in St. Louis, November 10-13, with headquarters at the Jefferson Hotel. The St. Louis Medical Society will act as host. A public session Monday evening will be addressed by Drs. James S. McLester, Birmingham, Ala., former President of the American Medical Association, on "Nutrition in War Time"; Mr. Edward A. Tamm, assistant director, Federal Bureau of Investigation, U. S. Department of Justice, Washington, D. C., "Espionage in the United States," and Dr. Frank H. Lahey, Boston, President of the American Medical Association, "Position of Medicine Today." Tuesday evening has been designated "President's Night"; speakers at this meeting will include Rev. Alphonse M. Schwitalla, S.J., St. Louis, who will give the invocation, and Dr. Paul H. Ringer, Asheville, N. C., president of the association, who will deliver an address entitled "Giants of Yesterday." Among the speakers will be:

Drs. Philip W. Brown, Louis A. Buie and Harry M. Weber, Rochester, Minn., An Unclassified Type of Ulcerative Disease of the Colon.
Dr. Nolan D. C. Lewis, New York, Biopsychiatry or Natural History of Psychiatry.
Dr. Martin H. Fischer, Cincinnati, Nature and Cause of Edema.
Dr. Waltman Walters, Rochester, Adrenal Tumors.
Dr. Lewis Clark Wagner, New York, Cysts of the Semilunar Cartilages: A Study of 40 Cases.
Drs. Ralph E. Campbell, Madison, Wis., and John L. McKelvey, Minneapolis, Chemotherapy in Obstetrics and Gynecology.
Dr. Oswald S. Lowsley, New York, Plastic Operations in Urology.
Dr. Louis J. Hirschman, Detroit, Some Pitfalls in Proctologic Diagnosis.
Dr. George P. Myers, Detroit, Hypertension in Train and Engine Service.
Drs. Ralph M. Tovell and Richard E. Edmondson, Hartford, Conn., Modern Concepts of Cyclopropane Anesthesia.
Dr. William H. Perkins, Philadelphia, Present Status of Teaching Preventive Medicine and Public Health in Our Medical Schools.

Drs. Cecil S. O'Brien, Iowa City, and Ernest M. Seydell, Wichita, Kan., will hold a round table discussion on "Staphylococcus Keratoconjunctivitis" and "Acute Otitis Media and Mastoiditis," respectively.

Deaths in Other Countries

Herbert Ritchie Spencer, consulting obstetric physician, University College Hospital, London, emeritus professor of obstetric medicine, University College, London; formerly president of Section of the History of Medicine and of Section of Obstetrics and Gynecology, Royal Society of Medicine; formerly president of the Medical Society of London; Harveian Orator in 1921; died August 28.——**Dr. Adalbert Czerny,** for many years professor of pediatrics at the University of Berlin, died, October 4, in Berlin, aged 78, according to a dispatch in the New York *Times*.——**Dr. L. C. Bailleul,** chief surgeon at the American Hospital of Paris since the death of Dr. Thierry de Martel at the time of the German occupation of Paris in June 1940, recently died in Paris, the *Times* reported September 26.

Government Services

Public Health Service Districts Reorganized

The U. S. Public Health Service districts, into which the United States and its territories are divided, have been reorganized so that there are now eight districts instead of six. The new districts and their directors are:

DISTRICT 1

Connecticut, Delaware, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont. Medical Director Claude C. Pierce, Sub-Treasury Building, 15 Pine Street, New York.

DISTRICT 2

District of Columbia, Maryland, North Carolina, Virginia, West Virginia. Senior Surg. Mark V. Ziegler, 25th & E Street N. W., Washington, D. C.

DISTRICT 3

Illinois, Indiana, Kentucky, Michigan, Ohio, Wisconsin. Medical Director Lon O. Weldon, Room 855 New Custom House, Chicago.

DISTRICT 4

Alabama, Florida, Georgia, Louisiana, Mississippi, South Carolina, Tennessee. Medical Director Charles L. Williams, 210 State Street, New Orleans.

SUBDISTRICT 4

New Mexico, Texas. Dr. Knox E. Miller, San Antonio.

DISTRICT 5

California, Nevada, Oregon, Washington, Alaska, Hawaii. Medical Director Richard H. Creel, Room 112, Federal Office Building, San Francisco.

DISTRICT 6

Puerto Rico, Virgin Islands. Senior Surg. Thomas H. D. Griffitts, San Juan, P. R.

DISTRICT 7

Arkansas, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, Oklahoma, South Dakota. Senior Surg. Calvin C. Applewhite, Rooms 601-612 Business Men's Assurance Company Building, 215 West Pershing Road, Kansas City, Mo.

DISTRICT 8

Arizona, Colorado, Idaho, Montana, Utah, Wyoming. Senior Surg. Lynne A. Fullerton, District Director, Rooms, 617-622, Colorado Building, Denver.

Foreign Letters

LONDON

(From Our Regular Correspondent)

Sept. 6, 1941.

The Bombing on London University

Much of the report on the work of the University of London during the year 1940-1941 by the principal, Mr. H. L. Eason, deals with the effects of the war on its academic life, teaching and research and on the buildings of the university. The intensive air raids on London have fully justified the policy of dispersal generally adopted in the summer of 1939. The damage to the university buildings has been so severe and widespread that if the schools had been able to continue their work in London the work of the university would have practically come to an end for the time being. But the constituent schools, which include those of the great hospitals, have also been severely damaged. University College has suffered very badly, and more recently the London School of Hygiene. The hospitals attached to the medical schools of the university have almost without exception been severely damaged. The greatest sufferers have been St. Bartholomew's and the London School of Medicine for Women. But in spite of the handicaps of war damage, decentralization and delays and difficulties of communication, the work of the university has been well maintained and normal examinations have been held, though in some cases in provincial centers where the hospitality of their universities and colleges has been extended to the University of London. The principal concludes: "This report deals in a scattered way with a scattered university. While exile has its disadvantages both for staff and students, it has its advantages in stimulating adaptability to circumstances and in providing education in methods, habits and customs of universities other than one's own. Our students and teachers have certainly not sat down by the waters of Babylon and wept." Such is the effect of the destruction wrought by the blitzkrieg on the highest activities of our civilization. The calculation was that the indiscriminate raining of thousands of tons of high explosive and incendiary bombs on the metropolis would break our spirit of resistance; it has only shown our powers of adaptation.

The Emergency Medical Services

The Emergency Medical Services have been established by the Ministry of Health to deal with the civilian casualties of the war. They have their own hospitals, medical centers and medical staffs, which include many of the leaders of the profession. Consultant advisers have been appointed to advise on the arrangements necessary to provide efficient treatment for different types of cases in emergency hospitals. Because of the dangers due to the bombing of London, much of the ministry's work has been decentralized and is carried out in regional offices. Eminent physicians and surgeons resident in the various regions have been selected to advise on the arrangements necessary for the efficient treatment of patients in the locality. In some cases the advisers appointed are consultants to the fighting forces stationed in the region. These include advisers on such special subjects as orthopedic surgery, chest wounds and head injuries. Twenty orthopedic centers are available for the treatment of orthopedic cases. For the treatment of injuries of the spinal cord and cauda equina, there is one special center in London and there are three in the provinces. There is even a special center for the diagnosis and treatment of patients presenting the effort syndrome. Ten regional consultants in thoracic surgery have been appointed and eleven in neurosurgery. For faciomaxillary injuries there are ten special centers. Mobile surgical teams have been organized to go to the assistance of hospitals other than their own in times of emergency. Some of these are special teams based on the appropriate special centers. The disposal of special head, chest and maxillofacial teams in an emergency is a matter for the respective consultant advisers to decide, and they may distribute the teams as they think best to meet the needs as they arise. The war organization of the British Red Cross and the Order of St. John of Jerusalem have undertaken to administer a number of auxiliary hospitals or convalescent homes as part of the Emergency Hospital Scheme. They are for the most part in private houses which are suitable only for postoperative, convalescent or other cases of comparatively mild involvement.

Venereal Diseases and the War

The record of previous wars has caused anxiety as to an increase of venereal diseases. At the Medical Society for the Study of Venereal Diseases Col. L. W. Harrison devoted his presidential address to a review of the present situation. He was able to state that since the outbreak of war the venereal diseases have not increased to anything like the extent feared. In 1939 the number of cases of early syphilis dealt with at the civilian treatment centers in England and Wales was 4,986, a decrease of 45 per cent since 1931 and less than a third of the number in 1920. The decline of the incidence of syphilis is also shown by a fall in the death rate due to the disease in infants from 2.03 per thousand in 1917 to 0.2 in 1939. The admission rate for syphilis in the navy stationed at home has fallen from 8.1 per thousand in 1921 to 1.96 in 1936, the last year for which figures are available. In the army the syphilis rate has fallen from 9.8 per thousand in 1921 to 0.9 in 1937. The returns from civilian clinics show that since the outbreak of war up to the end of March 1940 the fall in the syphilis rate slowed down, and that during the last twelve months there has been a definite increase in both males and females. Civilian cases of gonorrhea are fewer, but when service cases are added there is an increase of 9 to 10 per cent in males.

In the discussion which followed, the speakers maintained that there is only a slight increase in venereal diseases, except in the ports frequented by foreign seamen. In the army stationed at home the incidence has been uniform from week to week. The total rate for venereal diseases has fallen from 11.3 per thousand in 1938 to 8.7 in 1940 and 8.4 in the first five months of 1941. In the navy the return of syphilis is the lowest on record. There are now a large number of uniformed women in the auxiliary service of the navy and army. The amount of venereal disease among them is negligible.

Medical Libraries and the War

The war had a detrimental effect on medical libraries. The London ones have removed their more valuable contents to places which are safer from bombs but less accessible to readers. The Royal College of Surgeons, which has suffered much damage from bombs, took the precaution of removing a large part of its library to a place of safety which is too far away for readers. The Royal College of Physicians has had to store its library beyond access. The Royal Society of Medicine has evacuated about a third of its books within accessible reach of London. The London School of Hygiene has combined evacuation with limited accessibility. Another evil due to the war is that the medical libraries so much used for the reading of foreign periodicals are now almost devoid of them. Since the collapse of France periodicals have not been received from the countries overrun by the Germans, and very few are received from Germany. Thanks to the financial help of the Rockefeller Foundation, the Association of Special Libraries has undertaken a survey of the technical periodicals now reaching this country from abroad, so that those which are received will be available where they are most needed.

The Health of Children Improved by Migration to the Country

The anticipated bombing of our cities produced the great migration that began on Sept. 2, 1939, two days before the declaration of war. It involved the transfer to safer areas of 1,500,000 persons of whom half were children. By Christmas most of the evacuated children were receiving full time education in the reception areas. Then came the reaction, because of the lack of immediate danger, and many children returned home. But the fall of France and the intensification of air attacks stimulated fresh evacuation, and by December 1940 the number of children in reception areas, which had fallen to 472,000, rose to more than 620,000. The city children sent to country districts and allowed to settle down readily adapted themselves to the ways of their hosts and the conditions of rural life. Practically all improved in physique, general health, poise and bearing. Pure air, wholesome food and longer hours of sleep brought increase in weight and height, rosier cheeks and greater physical strength.

Health of Troops in the Middle East

In spite of a trying summer, the health of the troops in the Middle East is extremely good, according to the senior British medical officer. Not only is there a lower incidence than ever before of those diseases which are most common in mass formations of men in hot climates—dysentery, malaria, enteric fevers and cutaneous diseases—but men fresh from temperate climates, such as that of England, are standing up well to the heat. This satisfactory result has been obtained mainly by educating the troops by means of propaganda and by preventive measures. A vigorous anti-fly campaign has destroyed millions of flies and their breeding grounds. This has helped to keep down dysentery. Malaria cases have dropped from 3.5 per thousand to 0.58, and typhoid from 1.89 to 0.07. There has been no typhus fever.

RIO DE JANEIRO

(From Our Regular Correspondent)

Aug. 16, 1941.

Some Aspects of Syphilis in Rio de Janeiro

Syphilis is highly prevalent in Brazil, and Rio de Janeiro, the capital and largest city of the country, is no exception to the rule. At the start of the present century the crude annual death rate in Rio de Janeiro from the cause certified only as "syphilis" was about 10 per hundred thousand of population. A few years later this rate began to increase slowly to 12, to 15 and then to 20. The last mentioned figure corresponds to the epoch of the first world war, when syphilis had commenced to be a common subject of discussion, and the first plans to attack the disease in Brazil appeared in the medical periodicals and in the reports to the medical societies, particularly by the late Professors Werneck Machado and Eduardo Rabello. From then on the medical interest in the disease began to grow, and the increase of the death rate became still greater. A special division of venereal diseases was created in 1920 in the health department, and this was associated with even higher figures for the death rate from syphilis, which reached the peak of 60 deaths annually per hundred thousand in 1923. But this increase in the death rate, besides being attributable, among other factors, to the improvement in diagnosis, is a good example of transference of causes, as during the same period the annual crude rates for deaths related to the nervous and to the cardiovascular systems had shown a corresponding decline, from 230 to 80 per hundred thousand for the first group of causes, and from 307 to 182 for the second group. Then, from 1924 to the present, a reverse movement of the death rates was clearly shown by the statistical returns, syphilis with a declining trend and the nervous and cardiovascular systems with a rising trend. For the last three years the mean crude annual death rate from syphilis has been 36. Syphilis is recognized as a great factor in fetal deaths in Rio de Janeiro. During the last thirty years the fetal mortality rate has shown a fairly constant high level of about 75 per thousand total births, which is an indication of the great prevalence of syphilis. These figures have significance in the study of the incidence of mortality from syphilis. Thus for the last three years the mean crude annual death rate for the whole population of the city has been 36 per hundred thousand, while for Brazilians alone the rate has been 41 against 17 for the foreign population. For the age group 0-4 years the rate has been 350 as against only 5 for the age group 5-14 years, 6 for the age group 15-29 years and 35 for the age group 30 years and over.

Perhaps a better picture of the situation may be had from figures regarding patients found with syphilis in the clinics, hospitals and schools among those treated by the private practitioners. In a series of 20,000 persons of both sexes examined in a great outpatient clinic—the Policlinica Geral—4,943 have been found with syphilis (24.7 per cent), among whom 746 were in the early stage of the disease. In a series of 27,657 persons of both sexes examined from 1929 to 1939 at the outpatient department of the Gaffrée-Guinle Hospital, 5,631 (20.4 per cent) have been found with syphilis in different stages. Among thousands of patients treated during the latter few years in the large Santa Casa General Hospital, the number of cases of active syphilis or presenting visceral lesions caused by the disease has varied yearly from 18.2 per cent to 41.3 per cent of the total number of patients in the entire hospital. Dr. Martins Pereira, a public school physician, reported a few years ago 1,463 positive (27.5 per cent) Wassermann reactions in a total of 5,328 children attended in one of the school clinics of the city. In a recent paper Dr. Oscar Clark reported 653 cases of visceral and nervous lesions caused by syphilis, out of 2,000 consecutive recent adult patients of both sexes of his private practice (32.7 per cent). Similarly, Dr. G. Londres has found 22.6 per cent of positive serologic reactions in 1,000 consecutive male patients, among whom there were 181 in the early stage of the disease. The percentage of positive serologic reactions in pregnant women at large is considered a good index of the incidence of syphilis in the population. The figures for Denmark (Sieke), Australia (Fowler and Fairley) and the United States (Stillians), for instance, are pretty close, being respectively 6.7, 6.4 and 6.0, the latter relating to white women alone. It is interesting therefore to know that out of the total of 3,597 pregnant women attended in 1938 at the health centers of Rio de Janeiro 7.6 per cent had a positive Wassermann reaction. The Inhauma Health Center, serving a poor district of the city, reported 11.0 per cent of positive Wassermann reactions.

Marriages

W. WILSON SCHIER, New York, to DR. MADELINE BURLINGAME of Brooklyn, at Shelter Island Heights, L. I., August 16.

NICHOLAS HOWELL HOLMES, Chillicothe, Ohio, to Miss Jessie May Ullman of Waterford, Ohio, in Columbus in August.

FRANK C. WOMACK JR., Nashville, Tenn., to Miss Agnes L. Hightower, of Nacona, Texas, September 1.

EULYSS R. TROXLER to Miss Catherine Kirkpatrick, both of Greensboro, N. C., in Durham, August 20.

RAYMOND FRANKLIN SHEELY to Miss Margaret Elizabeth Zinn, both of Gettysburg, Pa., August 23.

LANCELOT W. ELLER, Kanawha, Iowa, to Miss Elizabeth Helen Moorhead of Fairfield, August 15.

JOHN H. WOODBRIDGE, Tchula, Miss., to Miss Trekrika Pittock of Portland, Ore., August 11.

MARVIN P. RHODES, New York, to Miss Helen Branson Strowd in Dayton, Ohio, recently.

Deaths

Howard Morrow ✠ San Francisco, vice president of the American Medical Association 1938-1939, died from a heart attack October 22, aged 66. Dr. Morrow was born in San Francisco. He received his degree in medicine at the University of California Medical Department in 1896. Subsequently he took up the specialty of dermatology and was professor of dermatology at his alma mater from 1911 to 1940. He was also a member and past president of the American Dermatological Association. He was a member of the American Academy of Dermatology and Syphilology, of the American Radium Society, of the Dermatological Association of Great Britain and Ireland and of the Vienna Dermatological Association. Dr. Morrow was active also in the affairs of the medical profession, serving as president of the California State Board of Public Health from 1933 to 1940 and as president of the California Medical Association in 1936. He was noted particularly for his work in the field of leprosy and had been for many years consultant to the United States Public Health Service. In his death medicine in the Far West loses one of its distinguished and most respected leaders.

Rudolf Schoenheimer, New York; Friedrich-Wilhelms Universität Medizinische Fakultät, Berlin, Prussia, 1922; Fellow of the Rockefeller Foundation working at Leipzig from 1923 to 1926; examiner on pathologic physiology for the German state board in 1928; Douglas Smith Fellow, working as research associate, department of surgery, Billings Hospital, University of Chicago, 1930-1931; head, department of pathologic chemistry, Pathological Institute, University of Freiburg from 1931 to 1933; member of the American Chemical Society and the Harvey Society; in 1937 gave a Harvey Lecture; in 1941 invited by Harvard University to give the Dunham Lectures (which were delivered posthumously); aged 43; was found dead, September 11, of poison, self administered.

Edmund Andrews ✠ Los Angeles; Rush Medical College, Chicago, 1915; member of the Illinois State Medical Society, American Surgical Association, Western Surgical Association, Society of Clinical Surgery and the Central Society for Clinical Research; fellow of the American College of Surgeons; at one time associate professor of surgery at the University of Illinois College of Medicine and professor of surgery at the University of Chicago, The School of Medicine; formerly vice president of the Chicago Academy of Sciences; served during the World War; at one time attending surgeon, Albert Merritt Billings Hospital, Chicago; aged 48; died, October 16, of coronary thrombosis.

Hans Louis Kleine ✠ St. Louis; Washington University School of Medicine, St. Louis, 1929; major, medical reserve corps, assigned to the medical detachment of the Sixty-Third Infantry; assistant in clinical obstetrics and gynecology at his alma mater; assistant obstetrician and gynecologist, Barnes and St. Louis Maternity hospitals; assistant obstetrician and gynecologist to outpatients, University Clinics; aged 35; died, September 21, at Natchitoches, La., of injuries received when he fell from a truck during army maneuvers.

Benjamin Frank Macnaughton, Montreal, Que., Canada; McGill University Faculty of Medicine, Montreal, 1915; member of the American Academy of Ophthalmology and Otolaryngology; served with the Royal Army Medical Corps during the World War; demonstrator of otolaryngology at his alma mater; served on the staff of the Montreal General Hospital in various capacities; aged 52; died, September 17, in the Western Division of the Montreal General Hospital.

Edward W. Mercer, Miami, Fla.; Hahnemann Medical College of Philadelphia, 1884; was demonstrator of histology and pathology from 1887 to 1890, demonstrator of obstetrics from 1890 to 1897 when he was made professor of obstetrics and held this chair until 1903; was senior obstetrician to the Hahnemann Hospital; aged 82; died, September 25.

Charles De Witt Colby, Asheville, N. C.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1892; member of the Medical Society of the State of North Carolina; member of the American College of Chest Physicians; veteran of the Spanish-American War; aged 75; died, September 23, of arteriosclerosis and heart disease.

Frank Cooley Phelps ✠ Vergennes, Vt.; University of Vermont College of Medicine, Burlington, 1893; past president of the Vermont State Medical Society; formerly mayor and city health officer; on the staffs of the Porter Memorial Hospital, Middlebury, and the Mary Fletcher Hospital, Burlington; aged 70; died, September 20.

Joseph Brown, Des Moines, Iowa; Baltimore Medical College, 1910; fellow of the American College of Surgeons; formerly on the associate staff of the Iowa Methodist, Mercy, and Iowa Lutheran hospitals and attending surgeon, Broadlawns General Hospital; aged 55; died, September 5, at Hollywood, Calif.

Frank Wesley Shipman, Mount Vernon, N. Y.; Bellevue Hospital Medical College, New York, 1893; for many years health officer of Mount Vernon; aged 71; served in various capacities on the staff of the Mount Vernon Hospital, where he died, September 20, of osteoporosis of the spine and pyonephrosis.

Allen Grant Flythe, Durant, Okla.; Jefferson Medical College of Philadelphia, 1921; member of the Oklahoma State Medical Association; assistant professor of pathology at the Baylor University College of Medicine, Dallas, Texas, 1923-1924; aged 45; died, September 21, of Rocky Mountain spotted fever.

James Ambrose Johnston, Cincinnati; Cincinnati College of Medicine and Surgery, 1881; past president of the Academy of Medicine of Cincinnati; fellow of the American College of Surgeons; formerly on the staff of St. Mary Hospital; aged 81; died, September 19, in the Christ Hospital of tuberculosis.

Alfred Winfield White, Brooklyn; Cornell University Medical College, New York, 1905; member of the Medical Society of the State of New York; fellow of the American College of Surgeons; aged 65; on the staff of St. John's Hospital, where he died, September 9, of nephritis.

Anatole Desjardins ✠ Wilkes-Barre, Pa.; Boston University School of Medicine, 1925; member of the Radiological Society of North America, Inc., and the American College of Radiology; on the staff of the Wilkes-Barre General Hospital; aged 48; hanged himself, September 18.

William Webster Harmer, Greeley, Colo.; Ohio Medical University, Columbus, 1900; member of the Colorado State Medical Society; past president of the Weld County Medical Society; on the staff of the Greeley Hospital; aged 69; died, August 21, of coronary thrombosis.

Philip Douglas Werum ✠ Toledo, Ohio; Chicago College of Medicine and Surgery, 1916; served during the World War; formerly on the staffs of the Robinwood Hospital and St. Vincent's Hospital; aged 54; died, September 3, in the Mercy Hospital of carcinoma of the lung.

George Eames Berrian, Jersey City, N. J.; Columbia University College of Physicians and Surgeons, New York, 1939; member of the West Virginia State Medical Association; on the staff of the Holden Hospital; aged 25; was found dead, September 14, at Holden, W. Va.

William F. Roberts ✠ Troy, Tenn.; University of Tennessee Medical Department, Nashville, 1894; past president and secretary of the Obion County Medical Society; formerly a bank president; aged 72; died, September 26, of pneumonia following a cerebral hemorrhage.

Ulysses Grant McElvain, Kansas City, Mo.; American Medical College, St. Louis, 1911; member of the Missouri State Medical Association; aged 71; died, September 24, in the Bethany Hospital, Kansas City, Kan., of chronic nephritis, arteriosclerosis and hypertension.

John Terrence Miller, Decatur, Ill.; Medical College of the State of South Carolina, Charleston, 1896; on the staffs of the Decatur and Macon County Hospital and the City Public Hospital; aged 69; died, September 23, in St. Mary's Hospital of lymphatic leukemia.

William George Rebec ✠ Belmont, Calif.; University of Michigan Medical School, Ann Arbor, 1925; medical director and superintendent of the Twin Pines Sanitarium; aged 44; died, September 10, at the Mills Memorial Hospital, San Mateo, of staphylococcic septicemia.

Margaret McKellar, Toronto, Ont., Canada; Queen's University Faculty of Medicine, Kingston, 1890; for many years a medical missionary in India under the Canadian Presbyterian Mission, and later the United Church; died, August 24, in the Toronto General Hospital.

Reinhardt W. Boerner, Milwaukee; Wisconsin College of Physicians and Surgeons, Milwaukee, 1896; member of the State Medical Society of Wisconsin; on the staff of St. Joseph's Hospital; aged 67; died, September 13, in the Milwaukee Hospital of diabetes mellitus.

William Sheffield Norton, Muscatine, Iowa; Kansas Medical College, Medical Department of Washburn College, Topeka, 1900; county coroner; past president of the board of education; served during the World War; aged 74; died, September 13, of coronary occlusion.

Robert **Graham** ✠ Duluth, Minn.; Detroit College of Medicine, 1893; for many years county physician; at various times on the staffs of St. Luke's Hospital and St. Mary's Hospital; aged 76; died, September 22, of carcinoma of the head of the pancreas.

Austin Byron Jones ✠ Kansas City, Mo.; St. Louis University School of Medicine, 1915; fellow of the American College of Physicians; on the staffs of the Menorah, Research and Kansas City General hospitals; aged 49; died, September 3, of heart disease.

Harry **Sherman Gossage,** Petaluma, Calif.; Cooper Medical College, San Francisco, 1893; for many years city councilman; at one time health officer; aged 72; died, September 8, at St. Helena Sanitarium and Hospital, Sanitarium, of cerebral hemorrhage.

David O'Quinn Du Bose, Andrews, S. C.; Maryland Medical College, Baltimore, 1909; member of the South Carolina Medical Association; member of the local and county school boards; aged 59; died, September 8, of coronary thrombosis.

Thomas Sisson Anderson, Live Oak, Fla.; Tallahassee College of Medicine and Surgery, Medical Department of the University of Florida, Jacksonville, 1886; member of the Florida Medical Association; aged 83; died, September 14, of myocarditis.

Roy Clayton Faust, Eugene, Ore.; Sioux City (Iowa) College of Medicine, 1905; member of the Oregon State Medical Society; aged 62; on the staff of the Sacred Heart Hospital, where he died, September 10, of hypertensive heart disease.

Stephen Girard Lee ✠ East Orange, N. J.; Bellevue Hospital Medical College, New York, 1898; aged 66; on the staff of the Orange (N. J.) Memorial Hospital, where he died, September 9, of acute cerebral embolism and coronary thrombosis.

William Bowler Hubbell ✠ Elyria, Ohio; University of Wooster Medical Department, Cleveland, 1898; served during the World War; on the staff of the Elyria Memorial Hospital; aged 66; died, September 26, of myelogenous leukemia.

Edson Andrew Blake, Waterloo, Que., Canada; McGill University Faculty of Medicine, Montreal, 1906; for many years chairman of the school board; aged 61; died, September 7, in the Royal Victoria Hospital, Montreal.

Clarence Albert Ransom ✠ East Falls Church, Va.; Johns Hopkins University School of Medicine, Baltimore, 1918; served during the World War; county coroner; aged 50; died, September 23, of a self-inflicted bullet wound.

Isaac Peirce, Tazewell, Va.; Jefferson Medical College of Philadelphia, 1888; member of the Medical Society of Virginia; aged 77; died, September 18, at the Bluefield (W. Va.) Sanitarium of gastric ulcer and hemorrhage.

Laura L. Liebhardt, Edgewater, Colo.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1884; aged 80; died in September of complications resulting from a fractured hip received in a fall.

Frederick William Munro ✠ Grosse Pointe, Mich.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1924; served during the World War; aged 41; died, September 15, in the Harper Hospital, Detroit.

Hugh Ellen Longino, Texarkana, Texas; University of Arkansas School of Medicine, Little Rock, 1916; member of the Arkansas Medical Society; served during the World War; aged 47; died, September 2.

Samuel Isaac Brody, Brooklyn; Universität Bern Medizinische Fakultät, Switzerland, 1937; first lieutenant, medical reserve corps, U. S. Army; aged 28; died, July 18, of subacute bacterial endocarditis.

Edward Harry Levy, Saranac Lake, N. Y.; Cornell University Medical College, New York, 1922; aged 42; died, September 24, in the New York State Hospital, Ray Brook, of pulmonary tuberculosis.

Houston Bate, Savannah, Tenn.; Meharry Medical College, Nashville, 1931; aged 38; died, September 27, in the Florida Agricultural and Mechanical College Hospital, Tallahassee, of cardiorenal disease.

Thomas Edward Waldie ✠ New York; Cornell University Medical College, New York, 1907; on the staff of the Misericordia Hospital; aged 56; died, September 18, in the Bellevue Hospital.

Robert Wellington Hall, Essex, Conn.; Bellevue Hospital Medical College, New York, 1894; formerly physician for the fire department of Brooklyn; aged 71; died, September 5, of heart disease.

Gregorio del Amo, Los Angeles; Universidad Central de España Facultad de Medicina, Madrid, Spain, 1878; aged 83; died, September 10, of bronchopneumonia and cerebral hemorrhage.

Charles Aylmer Fowler, Bend, Ore.; Chicago Medical College, 1884; city health officer; aged 83; died, September 17, at St. Charles Hospital of a fractured hip received in a fall.

Ernest Burnett, Hattieville, Ark.; College of Physicians and Surgeons, Little Rock, 1908; member of the Arkansas Medical Society; aged 59; died, September 13, of myocarditis.

Martin Henry Nester, Rogers City, Mich.; Detroit College of Medicine, 1904; for many years county school commissioner and county coroner; aged 71; died, September 18.

Herman J. Rickhoff, Hermann, Mo.; St. Louis College of Physicians and Surgeons, 1904; aged 63; died, September 17, in the Barnes Hospital, St. Louis, of cerebral hemorrhage.

Frank Chester Reynolds ✠ Chico, Calif.; University of Southern California School of Medicine, Los Angeles, 1935; aged 32; died in September of a self-inflicted bullet wound.

Wylie R. Holloway, Center Ridge, Ark.; University of Arkansas School of Medicine, Little Rock, 1907; member of the Arkansas Medical Society; aged 72; died, September 11.

Julius Michaelis, Brooklyn; Long Island College Hospital, Brooklyn, 1906; on the staff of the Samaritan Hospital; aged 66; died, September 20, of coronary thrombosis.

Samuel Koppelman, Newtown, Conn.; Temple University School of Medicine, Philadelphia, 1937; on the staff of the Fairfield State Hospital; aged 30; died, September 3.

Harold Walsworth Bell, Camden, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1902; aged 64; died, September 10, of coronary thrombosis.

Hubert Douglas Karass, Milwaukee; Wisconsin College of Physicians and Surgeons, Milwaukee, 1899; aged 62; died, September 17, of cerebral hemorrhage and nephritis.

John Warren Norman, St. Paris, Ohio; University of Cincinnati College of Medicine, 1917; served during the World War; aged 50; died, September 1, in Tampa, Fla.

Joseph Carl Kimball, Joliet, Ill.; Northwestern University Medical School, Chicago, 1908; aged 58; was killed, September 26, in an automobile accident.

William H. McCollum, Jonesboro, Tenn.; Louisville (Ky.) Medical College, 1892; member of the Tennessee State Medical Association; aged 73; died, September 4.

Herbert Henry Boyer ✠ Saylorsburg, Pa.; Medico-Chirurgical College of Philadelphia, 1912; aged 53; died, September 24, of cirrhosis of the liver.

Harvey Thompson Mounger, Hattiesburg, Miss.; University of the South Medical Department, Sewanee, Tenn., 1907; aged 61; died, September 6.

Charles Hooper Edwards, Moorhead, Miss.; Memphis (Tenn.) Hospital Medical College, 1902; aged 65; died, August 26, in Jackson of myocarditis.

William Price Davis Jr., Trumansburg, N. Y.; Jefferson Medical College of Philadelphia, 1904; aged 61; died, August 15, of valvular heart disease.

Henry John Luecke, Lexington, Ky.; Cincinnati College of Medicine and Surgery, 1901; aged 67; died, September 28, of injuries received in a fall.

John Frick, Memphis, Tenn.; Memphis Hospital Medical College, 1886; aged 75; died, September 18, in St. Joseph's Hospital of pneumonia.

Emily Walworth Fifield, Los Angeles; Woman's Medical College of Baltimore, 1884; aged 83; died, September 22, of cerebral hemorrhage.

John William King ✠ Hartington, Neb.; Detroit College of Medicine, 1886; aged 78; was found dead, August 27, of coronary occlusion.

Robert William Shaw, Aylmer (West) Ont., Canada; Trinity Medical College, Toronto, 1895; aged 70; died, August 23.

James Murray Patton, Vandergrift, Pa.; College of Physicians and Surgeons, Baltimore, 1885; aged 83; died, August 5, of senility.

Anton Liska, Chicago; Jenner Medical College, Chicago, 1909; aged 71; died, September 21, of cerebral hemorrhage.

Henry George Gibson, Glouster, Ohio; Starling Medical College, Columbus, 1898; aged 74; died, September 1.

Alexander R. Jarrett, Granbury, Texas; Atlanta (Ga.) Medical College, 1880; aged 85; died, September 1.

Nellie E. Green, Fowler, Ind. (licensed in Indiana in 1897); aged 98; died, September 3, of uremia.

Bureau of Investigation

REDUCTIO AD ABSURDUM

Dangerous Procedure Resurrected from the Dark Ages for the Treatment of Obesity

During the past year many inquiries have come to the Bureau of Investigation about the so-called Millet System of Reducing. An inquiry addressed to the concern which seemed to be back of the System, the Interstate Publishing Company, 105 North Clark Street, Chicago, brought a reply indicating that the method is one originally belonging to Miss E. Millet of New Orleans and maintained by her as a secret until the Interstate Publishing Company was able to persuade her that she could better herself financially by incorporating her method in their book. Attached to this information is an order blank for full instructions for $2.

In response to this order a mimeographed booklet is received entitled "The Millet System of Reducing" with a promise of another volume as soon as it is available. After calling attention to the fact that extensive exercises and diet are necessary to reduce the weight of the average person effectively and that steam baths, rubber girdles and such technics are merely temporary in their effect, the booklet affirms that it is necessary to consider something else and that, although the Millet system is drastic, it is at least practical. Frankly the promoters admit that when they first learned this secret they thought that it was too drastic and radical to be practical. Eventually, however, they were able to sell themselves on the idea of promoting the scheme at $2 per sixteen-page, double-spaced mimeographed leaflet or its equivalent, for those who ordered later received a more extensive volume (141 pages of similar material titled "Facts you should know about Reducing" by Harland LeRoy "Under the Auspices of Reducers Institute of America").

After a warning that many readers will be shocked and even horrified, they disclosed that the system consists of bloodletting. They call attention to the fact that bloodletting was once used erroneously for the treatment of disease, but the remainder of the material contains some interesting statements: "Today doctors know that any considerable loss of blood through injuries is always followed by a rapid loss of weight. This is known as acute or secondary anemia. It is a well known fact that anemic people are thin people. There are some types of anemia which does not cause loss of weight, but that is not the type of anemia caused by loss of blood." It is hoped that no one will engage in this bloodletting or allow himself to be a victim of it to the point at which he will develop the condition which the physicians refer to as acute or secondary anemia.

The booklet suggests the withdrawal of 8 to 16 ounces (240 to 480 cc.) of blood at a sitting and points out that a large person can give as much as a quart of blood for transfusion purposes and go about his regular occupation without ill effects; that professional blood donors have given hundreds of pints of blood, a pint at a time, and still remained strong and healthy (and weighty.—ED.).

In order to lure the prospective customer, the firm states: "To illustrate how little blood letting undermines the health, we cite the case of the Philadelphia professional strong man" who has given eight hundred and seventy-one blood transfusions and remains as strong as ever. The firm suggests that if you cannot afford the necessary doctor's fee, you have your name placed on the list of blood donors at some hospital nearby, and after getting a good start there you will have received enough money from the hospital to pay the physician's fees to continue the treatment, pointing out that hospitals, as a rule, will not take blood from a person more than once in six weeks and explaining, further, that "this is because a very high grade of blood is required for transfusion purposes, therefore the person desiring to reduce must take the rest of the treatments from a physician, or do the work themselves." They might also have added: "Therefore, the blood of an individual who is bled more frequently is of an inferior quality."

They then suggest that "it is possible for a person to withdraw blood enough from themselves to cause a rapid loss of weight." They describe this procedure but neglect to describe a sterile technic prior to the injection of the needle into the vein. They include a disclaimer to the effect that "before anyone should attempt to use the method upon themselves, it is advisable to offer their blood for transfusion purposes at some charitable hospital," in the first place, because it is valuable, and because they can learn how simple and easy bloodletting can be. They suggest that if home treatment is to be employed, a physician should be consulted to determine the amount which should be withdrawn.

They finally break down and confess that, like a drastic diet, the Millet System naturally leaves the user in a somewhat underpar condition for a while (mostly for as long as he continues the pernicious practice.—ED.). Therefore, according to the promoters, you should engage in it only when the weather is favorable, and also take "some good vitamin tablets" while under treatment. The promoters claim that another advantage of this system over unscientific dieting is that the body loses none of the necessary vitamins, minerals or other health-giving elements. Just exactly how this is accomplished while blood is taken as a routine from the body is a bit difficult to understand.

They conclude by stating that "Of course it is understood that once the desired weight has been attained by this method, the diet and amount of exercise must be regulated to maintain this weight," thus ending, as do all other proposed schemes for weight reduction, with the maintenance of a regimen which will permit the weight to be reduced or stay reduced. The concluding sentence is "Every overweight person knows that it is comparatively easy to keep from gaining weight, it is taking off weight that is such a futile task." This is an interesting conclusion, in view of the fact that they opened their presentation by calling attention to the fact that other methods of reducing were largely temporary in effect.

The information contained in this booklet is supposed to be worth $2—or, at least, that is the price one must pay to obtain it. Furthermore, in filling out the order blank for the book, one signs an agreement "not to disclose this Secret Method to anyone (my physician excepted)." An interested physician, however, thought little enough of this agreement which some one presumably made to forward a copy of the booklet to the Bureau.

The later book referred to above contained more extensive details of the inadequacy of other methods (not objecting strenuously however to "moderate" use of thyroid and benzedrine as directed by a physician) and also contained suggestions for "after treatment" which consisted of diet.

Various effective measures for the reduction of weight have been promoted which were detrimental and in some cases fatal to the persons who engaged in the procedure. In some respects the Millet System is similar to these. It is even reasonable to question whether or not the concern expects the purchaser to follow its method of reducing or is even interested at all beyond the receipt of the $2 for the booklet. Otherwise it is doubtful whether the promoters would call attention to the fact that hospitals would not withdraw blood frequently enough from the patient to produce a continued reduction in weight. If sufficient blood is allowed to escape from the system at regular and frequent intervals, there will be a reduction in weight. If the quantity removed and the frequency and regularity of removal are sufficient, death will ensue. The Millet System is a vicious plan for selling dangerous advice that intelligent people will not follow and that will inevitably harm those who do follow it. No doubt the Post Office Department and the Federal Trade Commission will find ways to terminate this pernicious performance.

Correspondence

HIGH LIGATION IN TREATMENT OF VARICOSE VEINS

To the Editor:—A communication to THE JOURNAL, August 16, page 553, by Dr. J. M. Hayes questions the safety of high ligation in the treatment of varicose veins. Instead, injection treatment is advocated in the upper part of the thigh as well as in the lower leg.

Pulmonary embolism is probably the chief hazard in the treatment of varicose veins. It was the cause of the high mortality of early radical surgical procedures (vein resection, vein stripping and so on), after which patients were of necessity bedfast. Later, with the development of ambulatory injection treatment, embolism became rare.

Obviously any form of treatment of varicose veins, whether by surgery, injection or ligation, involves the possibility of embolism, since all forms of treatment produce thrombi. But it seems unlikely that ambulatory ligation of the upper end of the great saphenous vein is more dangerous than the injection of sclerosing agents into the upper portion of the same vein without ligation. Just how does one limit clot formation in the upper end of the saphenous vein and prevent its propagation into the femoral vein?

Since 1934 I have been in charge of the varicose vein clinic at the Broadlawns General (Polk County) Hospital, Des Moines, Iowa. During this period the ligation treatment found increased usefulness. At present about 50 per cent of patients are treated by a high ligation (combined with low ligation when indicated) and retrograde injection. The remaining 50 per cent are treated by injection treatment alone. More than 100 patients have been submitted to ligation without mortality or serious complications. The good results obtained and the relative permanence of these results make me feel that ligation is a valuable and safe procedure, provided the following criteria are observed in selecting cases:

1. Patients with acute, subacute or latent phlebitis are potentially the most dangerous group. Ligation should not be performed on such patients for at least one year after subsidence of the last attack of phlebitis.

2. Patients with varicose ulcers should not be submitted to ligation. The ulcer should first be healed by supportive methods (Unna's boot and the like) to clear up any latent infection in the inguinal lymph nodes which might predispose to embolism.

3. Ligation should not be performed on pregnant women. I feel that the risk of precipitating thrombophlebitis or embolism is greater during pregnancy than at other times, because of stasis. Such patients are given supportive treatment (such as elastic bandages) until delivery. No treatment is advised for from three to six months post partum.

4. Ligation should not be performed on patients in poor physical condition, on the aged or on the obese.

The strict observance of these conditions has made ligation a safe procedure. As to permanence of results, ligation offers a greater chance of long term cure than injection alone. While ligation is not claimed as a permanent cure in all cases, recurrences over a five year period are rare, whereas it is common to see large varices return to their original condition one year after injection treatment alone.

Ligation with retrograde injection has been a definite advance in the treatment of varicose veins. The careful selection of patients for ligation is of the utmost importance in eliminating mortality and morbidity.

J. M. BRUNER, M.D., Des Moines, Iowa.

ECLAMPSIA

To the Editor:—The work of C. H. Burn, improved on by Griffith of the University of Pennsylvania, shows that there is such a thing as an antidiuretic principle which can be titrated by injection of blood into assay rats. Why could not this particular experiment be explained in this way: As the serum from the eclamptic donor is given, the antidiuretic level of the guinea pig in question is raised and raised so that a state of eclampsia exists in the guinea pig, a state of retention of the electrolytes sodium and potassium to the point of allery—allergy to anything. The antidiuretic level of the serum of the patient is a reflection of the activity of the pituitary of the eclamptic patient.

W. B. S. THOMAS, M.D., Dover-Foxcroft, Maine.

NOTE.—The essential point in Yamada's research is his experimental evidence of a primary denaturation of normal placental proteins in eclamptic patients, rendering these proteins highly antigenic for both man and experimental animals. Until such abnormal protein antigenicities are definitely ruled out, the so-called anaphylactic theory of puerperal eclampsia must be considered a theoretical possibility.—ED.

LEAD AND SILVER IN URINARY CALCULI

To the Editor:—In THE JOURNAL, July 5, 1941, page 20, Francis Carter Wood reported on studies he had made of the incidence of lead in urinary calculi. He drew attention to the finding by Trumper and Gordy (THE JOURNAL, March 29, 1941, p. 1389) of 3 per cent of lead in a phosphatic ureteral calculus while the urine contained lead in so-called normal amount. Dr. Wood compared the lead content of urinary stones of the vintage 1850-1860, examining 20, all of which contained lead, thus disproving any deduction that ethyl-lead gasoline necessarily accounts for increased lead output in the urine today. He also mentioned the fact that traces of copper and silver were regularly present, as well as other metals.

At a meeting of the Pathological Society of Eastern New York, Dec. 9, 1932, Dr. Gustavus H. Klinck Jr. (*Arch. Path.* **15**:751 [May], **16**:598 [Oct.] 1933), then my assistant in the Department of Pathology in Albany Medical College, reported a case of severe argyria in a woman aged 55 who had symptoms of a bladder disturbance. A roentgenogram showed a dense shadow occupying the entire area of the bladder. Dr. E. P. McDonald operated and removed a stone weighing 575 Gm. It was round, 10 cm. in diameter and dark red with pale yellowish laminations. Dr. A. P. Knudson, professor of biochemistry, examined various portions of the stone for silver but could find no trace of any.

Silver was demonstrated in the skin, and at autopsy several months later silver granules were found in many organs, although none could be seen in Kupffer's cells in the liver. The kidneys showed advanced pyelonephritis, but silver was abundant in or about the glomerular endothelium and along the basement membrane of the cortical tubules but not definitely in the cortical epithelium. The stroma of the medulla and cortex contained much silver, free and in phagocytes. The pelvis, ureters and bladder showed much chronic inflammation.

I must confess that, since there was much visible silver in the body and a large quantity in the kidney itself, we would not have been surprised to find the huge bladder stone harboring silver in ingot proportions, but it contained none. It was not tested for the presence of lead.

Some pathologists state that silver is deposited in tissues as an insoluble albuminate. Others do not commit themselves as to the molecular structure of the dark granule of argyria. Silver apparently is precipitated from solution by certain cells, especially fibroblasts in the medulla of the kidney, by smooth

muscle cells connected with hairs and around coil glands of the skin. At any rate, the lead molecule must be in more soluble form to be excreted by the kidney and thus is able to form part of urinary calculi. Silver oxide, or its albuminate, appears to be much less soluble and is largely confined to an extracellular position, so its absence from urinary calculi even as huge as that mentioned would seem to be explained. The microchemistry of argyria and plumbism, however, requires further study.

VICTOR C. JACOBSEN, M.D., Troy, N. Y.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

CHICAGO, Feb. 16-17, 1942. Council on Medical Education and Hospitals, Sec., Dr. William D. Cutter, 535 North Dearborn Street, Chicago.

MEDICAL CORPS, UNITED STATES NAVY

Examination. Assistant Surgeon with the permanent rank of Lieutenant (junior grade) and Acting Assistant Surgeon with the probationary rank of Lieutenant (junior grade), Jan. 5-9. Examination will be held at the Naval Hospitals at Chelsea, Mass., Newport, R. I., Brooklyn, Philadelphia, Norfolk, Va., Charleston, S. C., Pensacola, Fla., Corpus Christi, Tex., San Diego and Mare Island, Calif., Puget Sound, Wash., Great Lakes, Ill., Pearl Harbor, T. H., and Naval Medical Center, Washington, D. C. Apply Rear Admiral Ross T. McIntire, M.D., Surgeon General, U. S. Navy, Washington, D. C.

BOARDS OF MEDICAL EXAMINERS
BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Examinations of boards of medical examiners and boards of examiners in the basic sciences were published in THE JOURNAL, October 25, page 1462.

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Various centers, Feb. 9-11. Part III. Boston, November. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written. Part I.* Various centers, March 31. Final date for filing application is Dec. 31. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York City.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: *Oral.* Dec. 12-13. Final date for filing application is Nov. 8. Sec., Dr. C. Guy Lane, 416 Marlboro St., Boston.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* April in advance of the meeting of the American College of Physicians and June, in advance of the meeting of the American Medical Association. Applications should be on file 6 weeks in advance of the date of oral examination. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written. Part I. Group B.* Various centers, Jan. 3. *Oral. Part II. Groups A and B* Atlantic City, May or June. Final date for filing application is March 1. Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* March 7. Final date for filing application is Dec. 1. Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral and Written. All Groups.* Philadelphia, June, preceding the meeting of the American Medical Association. Final date for filing application is March 1. Sec., Dr. W. P. Wherry, 1500 Medical Arts Bldg., Omaha, Neb.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Philadelphia, March or April, at the time of the Region I meeting of the American Academy of Pediatrics. Cleveland, May, at the time of the Region III meeting of the American Academy of Pediatrics. Los Angeles, May, at the time of the Region IV meeting of the American Academy of Pediatrics. *Written.* Locally, approximately 6 weeks in advance of the date of oral examination. Sec., Dr. C. A. Aldrich, 707 Fullerton Ave., Chicago.

AMERICAN BOARD OF RADIOLOGY: *Oral. All Groups.* Atlantic City, June 4. Final date for filing application is April 1. Sec., Dr. Byrl R. Kirklin, 102-110 Second Ave., S. W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Oral. Part II.* New York Nov. 10-11. A meeting of the board will follow on the 12th. Sec., Dr. J. Stewart Rodman, 225 S. Fifteenth St., Philadelphia.

AMERICAN BOARD OF UROLOGY: *Written.* Various centers, December. Sec., Dr. Gilbert J. Thomas, 1009 Nicollet Ave., Minneapolis.

California Reciprocity Report

The Board of Medical Examiners of the State of California reports 63 physicians licensed to practice medicine by reciprocity and 10 physicians so licensed by endorsement from January 2 through July 12. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Yale University School of Medicine		(1935)	Penna.
Howard University College of Medicine		(1930)	Kansas
Emory University School of Medicine		(1917)	S. Carolina, (1937) Georgia
Chicago College of Medicine and Surgery		(1915)	Missouri
Loyola University School of Medicine		(1929)	Montana, (1934) New Jersey, (1939) Illinois
Northwestern University Medical School		(1900)	Illinois, (1925) New York, (1932) Oklahoma, (1939) Utah
Rush Medical College		(1919)	Michigan, (1928) Illinois
The School of Medicine of the Division of the Biological Sciences		(1936)	New York, (1938) Illinois
University of Illinois College of Medicine		(1927)	Wisconsin, (1936) Michigan
State University of Iowa College of Medicine		(1935),	(1938) Iowa
University of Kansas School of Medicine		(1934)	Missouri
University of Louisville School of Medicine		(1934)	Ohio, (1937) North Dakota
Louisiana State University Medical Center		(1936)	Louisiana
Tulane University of Louisiana School of Medicine		(1936)	Louisiana
University of Maryland School of Medicine and College of Physicians and Surgeons		(1932)	New York
Harvard Medical School		(1937)	Maryland
University of Minnesota Medical School		(1914),	(1925), (1934, 2), (1935), (1937) Minnesota, (1932) Ohio
St. Louis University School of Medicine		(1930)	Oregon, (1927), (1931), (1937) Missouri
Washington University School of Medicine		(1938)	Missouri
Creighton University College of Medicine		(1931)	Nebraska
Lincoln Medical College of Cotner University		(1908)	Nebraska
University of Nebraska College of Medicine		(1920),	(1930) Nebraska, (1931) Washington
Columbia University College of Physicians and Surgeons		(1934)	W. Virginia
New York University College of Medicine		(1936),	(1938) New York
University and Bellevue Hospital Medical College		(1911),	(1917), (1925) New York
Ohio State University College of Medicine		(1923)	Ohio
Western Reserve University School of Medicine		(1933)	Ohio
University of Oklahoma School of Medicine		(1936)	Oklahoma
University of Oregon Medical School		(1934),	(1937) Oregon
University of Pennsylvania School of Medicine		(1925)	N. Dakota, (1937) Pennsylvania
University of Tennessee College of Medicine		(1919)	Tennessee
Marquette University School of Medicine		(1930, 2)	Wisconsin
University of Manitoba Faculty of Medicine		(1936)	S. Dakota
University of Edinburgh Faculty of Medicine		(1919)	Nebraska, (1937) Pennsylvania

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
College of Medical Evangelists		(1938)	N. B. M. Ex.
Rush Medical College		(1915)	N. B. M. Ex.
Harvard Medical School		(1936)	N. B. M. Ex.
Washington University School of Medicine		(1934)	U. S. Navy
Cornell University Medical College		(1929)	N. B. M. Ex.
Duke University School of Medicine		(1934)	N. B. M. Ex.
Jefferson Medical College of Philadelphia		(1919)	U. S. Navy
University of Pennsylvania School of Medicine		(1929)	N. B. M. Ex.
Vanderbilt University School of Medicine		(1931)	N. B. M. Ex.
University of Toronto Faculty of Medicine		(1927)	N. B. M. Ex.

California Reciprocity Report

The Board of Medical Examiners of the State of California reports 56 physicians licensed to practice medicine by reciprocity and 2 physicians so licensed by endorsement from July 15 through August 14. The following schools were represented:

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
College of Medical Evangelists		(1939)	Michigan
University of Colorado School of Medicine		(1939),	(1940) Colorado
Yale University School of Medicine		(1909)	R. Island, (1930) New York, (1932) Connecticut
Loyola University School of Medicine		(1932)	Illinois
Northwestern University Medical School		(1933)	Kansas
Rush Medical College		(1932)	Minnesota, (1928), (1932) Illinois
University of Illinois College of Medicine		(1935)	Illinois
State University of Iowa College of Medicine		(1925)	Iowa
Univ. of Kansas School of Med.		(1934, 2),	(1937), (1940, 2) Kansas
Southwestern Homeopathic Medical College and Hospital, Louisville		(1904)	Kentucky
Johns Hopkins Univ. School of Med.		(1925),	(1931), (1935) Maryland
Harvard Medical School		(1931)	Mass.
University of Michigan Medical School		(1931)	Michigan
Wayne University College of Medicine		(1934)	New York
Univ. of Minnesota Medical School		(1926),	(1935), (1939) Minnesota
St. Louis University School of Medicine		(1926)	Utah
Washington University School of Medicine		(1931)	Missouri
John A. Creighton Medical College		(1914)	Iowa, (1915) Wyoming
Univ. of Nebraska College of Med.		(1921),	(1929), (1933) Nebraska
Columbia Univ. College of Physicians and Surgeons			(1937) Utah
Cornell University Medical College		(1935)	R. Island
New York Homeopathic Medical College and Flower Hospital		(1928)	New York
University of Buffalo School of Medicine		(1909)	New York
Univ. of Rochester School of Medicine and Dentistry		(1937)	New York
Ohio State University College of Medicine		(1930)	Penna.
University of Cincinnati College of Medicine		(1916),	(1930) Ohio, (1935) Minnesota
Western Reserve Univ. School of Med.		(1932),	(1933), (1935) Ohio
Medico-Chirurgical College of Philadelphia		(1899)	Penna.
Univ. of Pennsylvania School of Med.		(1911)	Penna., (1936) Ohio
Woman's Medical College of Pennsylvania		(1933)	New York
Vanderbilt University School of Medicine		(1935)	N. Carolina
Medical College of Virginia		(1934)	Virginia
Marquette University School of Medicine		(1931)	Wisconsin
University of Wisconsin Medical School		(1935)	Wisconsin
First Moscow Medical Institute		(1919)	Minnesota

School	LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
Washington University School of Medicine		(1929)	N. B. M. Ex.
University of Pennsylvania School of Medicine		(1924)	Hawaii

Maine July Report

The State of Maine Board of Registration of Medicine reports the written examination for medical licensure held at Augusta, July 1-2, 1941. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Sixteen candidates were examined, 14 of whom passed and 2 failed. Seven physicians were licensed to practice medicine by reciprocity and 3 physicians so licensed on endorsement of credentials of the National Board of Medical Examiners. The following schools were represented:

School	PASSED	Year Grad.	Number Passed
Harvard Medical School		(1933), (1941)	2
Tufts College Medical School		(1940)	1
Columbia University College of Physicians and Surgeons		(1931), (1940)	2
Hahnemann Med. College and Hospital of Philadelphia		(1940)	1
Temple University School of Medicine		(1941)	1
University of Pennsylvania School of Medicine (1940),		(1941)	2
Laval University Faculty of Medicine		(1940)	1
Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg		(1936)	1
Medizinische Fakultät der Universität Wien		(1938)	1
Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest		(1930)	1
Licentiate of the Royal College of Physicians, of the Royal College of Surgeons of Edinburgh and of the Royal Faculty of Physicians and Surgeons, Glasgow		(1935)	1

School	FAILED	Year Grad.
University of Montreal Faculty of Medicine		(1941)
Regia Università degli Studi di Padova. Facoltà di Medicina e Chirurgia		(1936)

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Yale University School of Medicine		(1904)	Dist. Colum.
University of Maryland School of Medicine and College of Physicians and Surgeons		(1935), (1937)	Maryland
Harvard Medical School		(1936)	Penna.
University of Michigan Medical School		(1935)	Michigan
McGill University Faculty of Medicine		(1925)	Maryland
Medizinischue Fakultät der Universität Wien		(1920)	Maryland

School	LICENSED BY ENDORSEMENT	Year Grad.
Harvard Medical School		(1925), (1934), (1939)

Minnesota June Report

The Minnesota State Board of Medical Examiners reports the written examination for medical licensure held at Minneapolis, June 17-19, 1941. The examination covered 12 subjects and included 60 questions. An average of 75 per cent was required to pass. Fifty-eight candidates were examined, all of whom passed. Three physicians were licensed to practice medicine by reciprocity and 4 physicians so licensed on endorsement of credentials of the National Board of Medical Examiners. The following schools were represented:

School	PASSED	Year Grad.	Number Passed
University of Colorado School of Medicine		(1935)	1
Northwestern University Medical School		(1940), (1941)	2
Rush Medical College		(1939)	1
University of Louisville School of Medicine		(1939)	1
Johns Hopkins University School of Medicine		(1941)	1
Harvard Medical School		(1938)	1
Universtiy of Minnesota Medical School (1940, 4), (1940, 2),* (1941, 6), (1941, 23)*			35
Creighton University School of Medicine		(1941)	1
University of Nebraska College of Medicine		(1938)	1
Columbia Univ. College of Physicians and Surgeons		(1941)	1
Syracuse University College of Medicine		(1938)	1
Hahnemann Med. College and Hospital of Philadelphia		(1940)	1
University of Texas Faculty of Medicine		(1939)	1
Medical College of Virginia		(1938)	1
Marquette University School of Medicine		(1941, 2)	2
University of Wisconsin Medical School		(1939), (1940, 3)	4
University of Manitoba Faculty of Medicine		(1939), (1941)	2
McGill University Faculty of Medicine		(1937)	1

School	LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
Rush Medical College		(1934)	Wisconsin
State University of Iowa College of Medicine		(1939)	Iowa
Marquette University School of Medicine		(1926)	Wisconsin

School	LICENSED BY ENDORSEMENT	Year Grad.
Harvard Medical School		(1936), (1939)
Duke University School of Medicine		(1937)
University of Pennsylvania School of Medicine		(1940)

* These applicants received the M.B. degree and will receive the M.D. degree on completion of internship.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Governmental Hospitals: Operation of Hospital by County a Governmental, Not a Proprietary, Function.—The plaintiff brought an action for damages against the County of Colusa (Calif.), the board of supervisors of that county, the director of the county hospital (a physician) and two nurses employed in the hospital. She alleged that the county maintained in a proprietary capacity a hospital which was under the management and control of the board of supervisors of the county, that, requiring immediate hospitalization and emergency treatment, she was admitted to the hospital as a pay patient and while a patient therein "and in need of constant nursing, care and attention, and while in a state of delirium from fever and illness, and while wholly unconscious, the defendants failed to render such necessary care and attention by leaving plaintiff unattended, and as a result thereof she fell from her bed in the hospital and was injured." Demurrers interposed by all the defendants were sustained by the trial court, and the plaintiff appealed to the district court of appeal, third district, California.

The demurrers interposed by the county and by the board of supervisors were based essentially on a rule of law assumed by the trial court that a county cannot be sued for acts arising out of its performance of a governmental function and that the county in operating a hospital was performing a governmental function. The plaintiff contended, however, that the demurrers were improperly sustained, since in her complaint she alleged that the hospital wherein she was injured was operated in a proprietary capacity by the county, and that the defendants by demurring to her complaint admitted the truth of that allegation, that is, admitted that the hospital was operated in a proprietary capacity. If the hospital actually was operated in a proprietary capacity by the county, the county would have been liable for damages occasioned by the negligence of its servants and agents. The general rule of pleading, however, said the district court of appeal, on which the plaintiff's contention is based, does not admit a conclusion of law, nor does it admit the construction placed on an instrument pleaded in the complaint, or facts impossible in law, or allegations contrary to facts of which a court may take judicial knowledge. In this case the allegation by the plaintiff that the hospital was operated in a proprietary capacity by the county was not admitted by the demurrers interposed, since it has been previously held by the Supreme Court of this state that the operation of a county hospital is a governmental function. *Sherbourne* v. *Yuba County*, 21 Cal. 113, 81 Am. Dec. 151. The complaint in this case, moreover, continued the court, further alleges that the county hospital was maintained and conducted by the county for the purpose of furnishing hospitalization to the following persons: first, to all indigent sick in the county free of cost; second, to all resident veterans and their dependents free of cost; third, to other residents of the county as the facilities would permit on the payment of the cost of hospitalization, and, fourth, in the case of an emergency to any one needing attention. In addition, remarked the court, any expectant mother who is unable to pay for her necessary care must also be admitted to the hospital. From these classifications it would appear that the county was conducting a general public hospital and that it cannot be held as a matter of law that the hospital was conducted in a proprietary capacity, regardless of any allegations to that effect in the complaint. The fact that the hospital admitted certain paying patients did not convert a public hospital into a proprietary or private hospital. The court accordingly concluded that the hospital was operated by the county in a governmental capacity and that the demurrers with respect

to the county and to the board of supervisors were properly sustained.

The court next considered the propriety of the trial court's action in sustaining the demurrer interposed by the physician-director of the hospital. The gist of the complaint, said the court, against the physician-director is that he was negligent in his supervision of the nurses, but he as director did not apparently select or employ these nurses, nor was he, as director, responsible to the plaintiff for any failure of supervision but was answerable only to the county that employed him. As indicative of the director's liability, the plaintiff referred to *Davie* v. *Board of Regents*, 66 Cal. App. 689, 227 P. 247, which held that, even if the regents of a university which conducted a hospital were not liable for the tort of an employee of the university, nevertheless the employees themselves were individually chargeable with such negligence, and that it made no difference whether the hospital conducted by the university and of which the negligent employees were employed was being conducted in a proprietary capacity or as a governmental function. That is true, said the court, where the injuries resulted from the negligent care and treatment of the patient by the employees, but here the director was not alleged to have had the care of the plaintiff—that duty resting on the attendants of the hospital—and the injuries sustained by the plaintiff had nothing to do with the lack of skill or care of the director of the hospital. Therefore, since the personal care of the plaintiff was not on the physician-director, since there is no allegation that he directed the nurses to do or refrain from doing anything that caused harm to the plaintiff and since there was no contract between the plaintiff and the physician-director, there was no cause of action stated against him.

The situation of the defendant nurses, continued the court, however, is somewhat different from that of the physician-director. The care and attention of the plaintiff was personally entrusted to them, and the complaint alleges that they failed to render such service. When one has undertaken to render assistance or care, even if a volunteer, the law imposes a duty of care toward the person assisted. The district court of appeal concluded that the trial court should have overruled the demurrers of the two defendant nurses and required them to answer.

Accordingly, the judgment in favor of the defendants county, the board of supervisors and the physician-director of the hospital was affirmed and that portion of the judgment in favor of the nurses was reversed, with the right given them to plead further.—*Griffin v. Colusa County, 113 P. 2d. 270 (Calif., 1941).*

Society Proceedings

COMING MEETINGS

American College of Surgeons, Boston, Nov. 3-7. Dr. Frederic A. Besley, 40 East Erie St., Chicago, Secretary.

American Society of Tropical Medicine, St. Louis, Nov. 11-14. Dr. E. Harold Hinman, Wilson Dam, Ala., Secretary.

Annual Conference of Secretaries of Constituent State Medical Associations, Chicago, Nov. 14-15. Dr. Olin West, 535 N. Dearborn St., Chicago, Secretary.

Associated Anesthetists of the United States and Canada, Boston, Nov. 3-7. Dr. C. J. Wells, 1932 S. Salina St., Syracuse, N. Y., Secretary.

Central Society for Clinical Research, Chicago, Nov. 7-8. Dr. Carl V. Moore, Washington University School of Medicine, St. Louis, Secretary.

National Society for the Prevention of Blindness, New York, Dec. 4-6. Mrs. Eleanor Brown Merrill, 1790 Broadway, New York, Executive Director.

Puerto Rico, Medical Association of, Santurce, Dec. 11-14. Dr. David E. Garcia, P. O. Box 3866, Santurce, Secretary.

Radiological Society of North America, San Francisco, Dec. 1-5. Dr. Donald S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y., Secretary.

Society for the Study of Asthma and Allied Conditions, New York, Dec. 6. Dr. W. C. Spain, 116 East 53d St., New York, Secretary.

Southern Medical Association, St. Louis, Nov. 10-13. Mr. C. P. Loranz, Empire Bldg., Birmingham, Ala., Secretary.

Southern Surgical Association, Pinehurst, N. C., Dec. 9-11. Dr. E. Alton Ochsner, 1430 Tulane Ave., New Orleans, Secretary.

Southwestern Medical Association, El Paso, Texas, Nov. 20-22. Dr. Louis W. Breck, 116 Mills St., El Paso, Secretary.

Western Surgical Association, St. Paul, Dec. 5-6. Dr. Arthur R. Metz, 2449 Washington Blvd., Chicago, Secretary.

THE AMERICAN RHEUMATISM ASSOCIATION

Eighth Annual Meeting, held in Cleveland, June 2, 1941

DR. A. R. SHANDS JR., Wilmington, Del., Secretary

Gold Therapy in Rheumatoid Arthritis: Presidential Address

DR. RALPH H. BOOTS, New York: As the four papers in this symposium on chrysotherapy to be presented are reports of experimental studies, it seems fitting to review briefly our present knowledge of gold therapy, especially its dangers and limitations, so that it does not fall into the status of another cure for rheumatism and suffer the fate of the many previous "fads." Too often the harmful effects of a new drug outweigh its therapeutic effect. The preparations used today are toxic in 25 to 40 per cent of the cases, and it is timely to emphasize their dangers and the fact that they have been recommended only in one type of arthritis, namely rheumatoid arthritis.

According to Parr and Shipton, the use of gold in medicine dates back at least to the eighth century, when Abu Moussa the Wise recommended it as a cureall for every known disease. Paracelsus, the alchemist and chemist, in about the year 1500 A. D., recommended a so-called elixir of life, which was composed of gold and mercury, and gold was first used for tuberculosis in his time. Owing to serious accidents, it was dropped until many years later.

In recent time, gold therapy, or chrysotherapy, had been recommended for tuberculosis and cutaneous diseases before its use was proposed in rheumatoid arthritis by Feldt. Schiemann and Feldt in 1926 found that certain organic gold compounds produced, on subcutaneous injection, a distinct therapeutic effect on streptococcic infections in mice. Feldt also showed that compounds in which the gold was bound through a sulfhydryl group were most effective. All the gold preparations in use today make use of this principle. Recently Dawson and Hobby, using gold sodium thiomalate, have demonstrated definite chemotherapeutic properties against experimental hemolytic streptococcus infections in mice. Collier found the same and also that gold preparations were of value in treating polyarthritis in mice whose joints were probably infected with pleuropneumonia organisms.

A number of explanations have been offered for the beneficial action of gold salts in rheumatoid arthritis. Until recently the most popular was that it stimulated the reticuloendothelial system. In view of recent bacteriologic and immunologic studies, it would seem that it might have a direct chemotherapeutic effect on the causative agent.

Forestier was the first to popularize the use of gold salts in rheumatoid arthritis. He argued that "if gold salts are active in a chronic disease like human tuberculosis, why should they not be active in another chronic disease in which an important infectious factor seems to be present?" At that time some French authorities regarded rheumatoid arthritis as having a tuberculous etiology. This was the basis of his conception and the start of his use of gold salts in the treatment of arthritis. He attempted to arouse interest in his work in America in 1934. Following his visit here we treated a small number of patients in this manner. The sixth patient treated developed such severe exfoliative dermatitis that we considered the therapy too toxic and gave it up until 1938, when English investigators caused an increased interest by their enthusiastic reports. Since then numerous papers on this subject have appeared in this country. According to a recent personal communication Dr. Forestier is still enthusiastic about gold therapy, after thirteen years.

As a result of the experience of others and three years' experimental trial of chysotherapy in the Arthritis Clinic at the Presbyterian Hospital, New York City, I have come to believe the following:

1. This form of therapy offers definite promise in the treatment of rheumatoid arthritis.

2. Gold salt therapy should not be recommended for any form of arthritis except rheumatoid. Because of its toxicity, only proved cases of rheumatoid arthritis justify its use.

3. No more than two thirds of the patients are able to tolerate full courses of the drug, and of these about 50 per cent exhibit striking improvement. In other words, we look for such improvement in 33 per cent of our rheumatoid arthritis cases. By striking improvement is meant a decided objective and subjective change in the patient, accompanied by a convincing drop in the blood sedimentation rate. This degree of improvement represents a change which, in our experience, occurs only rarely, either spontaneously or as a result of any other therapeutic procedure.

4. Although chrysotherapy offers great promise today, in its present form it should not be regarded as the cure for rheumatoid arthritis, and it would seem imperative that great emphasis be placed on those other forms of treatment which in former years have been shown to be of real value, namely rest, nutrition, transfusions, removal of infections, climate, prevention of deformities and physical therapy.

5. Any physician contemplating the use of gold should visit one of the clinics which is using this form of therapy and acquaint himself with the toxic reactions, as I am sure that an intimate knowledge of the early appearance of these reactions is necessary to lessen the percentage of those of the severer types.

6. The future of gold salts lies largely in the hands of the chemists. It would seem that in the future a more active and less toxic preparation might be produced. Until then, despite its real value, its popularity will have its ups and downs, depending on the number of toxic reactions encountered by any individual physician.

The Influence of Gold Sodium Thiomalate (Myocrysin) on the Prevention and Cure of Hemolytic Streptococcus Arthritis in Rats

DRS. SIDNEY ROTHBARD, D. MURRAY ANGEVINE and RUSSELL L. CECIL, New York: Previous experiments have revealed that a strain of hemolytic streptococcus would induce arthritis on intravenous injection in 100 per cent of animals. Gold sodium thiomalate was found to be effective in the prevention of this disease but was not so effective against a more virulent culture of the same strain. Sulfanilamide and sulfathiazole were found to be as effective in the prevention of this disease as the gold salt. Gold and sulfonamide compounds did not have a curative effect on the arthritis. Although gold was found to be bactericidal in vitro, experiments in vivo showed no difference in the number of bacteria in the peripheral blood, bone marrow, liver and spleen of treated and nontreated animals.

Observations were made on the toxic effects of gold sodium thiomalate given to animals over various periods of time. Complete blood studies revealed eosinophilia in the peripheral blood of all the animals injected with gold over a prolonged period. A severe renal injury that resulted in the death of the animal was observed after an injection of 15 mg. or more of gold. As little as 0.5 mg. produced renal damage in 75 per cent of the rats, whereas 1 mg. or more produced it in every instance. Gold was observed microscopically within the cells and lumens of the renal tubules.

From these studies it appears that gold sodium thiomalate protects rats against hemolytic streptococcus arthritis but does not cure it. Since the effective dose is so close to the lethal dose, great caution is necessary in its administration.

The Curative Effect of Gold Salts in Experimental Chronic Arthritis of Mice with Special Reference to the Properties of Calcium Aurothiomalate

DR. ALBERT B. SABIN and JOEL WARREN, PH.D., Cincinnati: The experimental disease produced in mice by the type B mouse pleuropneumonia micro-organism differs from the experimental arthritis caused by pyogenic micro-organisms (whether bacterial or of the rat pleuropneumonia group) in that it is a progressive, chronic, essentially proliferative arthritis which in its clinical and pathologic manifestations bears a certain resemblance to human rheumatoid arthritis. Chemotherapeutic studies carried out in the past two years revealed that, of many compounds tested, only those which contained gold in a dissociable and chemically reactive state (i. e., noncolloidal) were capable of exerting a curative effect. With treatment started early after the appearance of arthritis and with adequate doses of gold salts it has been possible to obtain a complete and persistent curative effect in nearly 100 per cent of mice. As the dose approaches the minimal range the number of treated animals which lose their arthritis becomes smaller and the incidence of spontaneous recurrences after cessation of therapy is definitely increased. The arthritis disappeared completely within eight weeks or less after the beginning of therapy in 86 per cent of 603 mice treated with suitable gold compounds at the proper time, but only in 21 per cent of 403 mice receiving the same compounds in less than minimal effective dosage or too late in the disease, and in only 5 per cent of 100 mice receiving ineffective compounds including colloidal gold, sodium salicylate, bismuth subsalicylate, fuadin (antimony), neoarsphenamine, silver arsphenamine, sulfapyridine and sulfathiazole; among the 184 mice which served as the untreated controls in these tests the arthritis disappeared spontaneously in only 6 per cent.

A study of the influence of chemical structure of gold compounds on their toxicity as measured by the lethal effect on 20 Gm. mice revealed that toxicity depended not on the concentration of gold in a given compound but rather on the nature of the radical to which the gold is attached and on the solubility or relative insolubility of the compound. However, while it was found that some gold compounds could be one hundred times more toxic than others, there was relatively little variation in the minimal therapeutic dose, especially among the soluble compounds. Of all the substances tested, calcium aurothiomalate was found to possess the greatest margin of safety as a chemotherapeutic agent. Of the three insoluble gold compounds studied, i. e. calcium aurothioglycollate, calcium aurothiomalate and aurothioglycoanilide, all were tolerated when as much as 100 mg. (or 5 Gm. per kilogram) was injected subcutaneously or intramuscularly in a single dose to 20 Gm. mice, but they were not all equally effective as therapeutic agents. Thus, the minimal therapeutically effective amount administered as a single dose was 5 to 10 mg. for calcium aurothioglycollate, about 10 mg. for aurothioglycoanilide but only 0.5 mg. for calcium aurothiomalate, and its curative effect appeared in almost one third of the time required by the other two. Calcium aurothiomalate was also the only insoluble compound whose minimal therapeutic dose was smaller than that of any of the soluble compounds tested. The minimal therapeutic amount of sodium aurothiomalate, administered as a single dose, was found to be about four times as large as that of the calcium salt, while the amount of calcium aurothiomalate tolerated by nearly all mice was twenty to fifty times greater than that of the sodium salt. The margin of "complete" safety was thus found to be at least one hundred times greater for calcium aurothiomalate than for sodium aurothiomalate.

Gold Metabolism and the Fate of Gold Injected in the Treatment of Arthritis

DR. R. H. FREYBERG, W. D. BLOCK, PH.D., and O. H. BUCHANAN, M.S., Ann Arbor, Mich.: While patients with rheumatoid arthritis were receiving increasing amounts of gold sodium thiomalate, gold sodium thiosulfate or aurol sulfide at weekly intervals (for approximately six weeks) the concentration of gold in the blood and the urinary, and in some cases the fecal, excretion of gold were measured daily by means of a new, highly sensitive, photoelectric colorimetric method. In addition, on the day of administration of the gold salt the blood and urine content of gold was determined one, two, four, six and twenty-four hours after injection. After the weekly dose became standardized, similar determinations of gold were made at intervals throughout the period of treatment and for several months thereafter. Occasionally the concentration of gold in synovial fluid and blood were measured simultaneously. In many other patients occasional determinations of gold in blood and urine were made during and after periods of chrysotherapy.

Gold metabolism and excretion studies have been carried out on patients during and after the administration of gold sodium

thiomalate, gold sodium thiosulfate and colloidal gold sulfide. Gold in the blood was always found to be in the plasma. It is eliminated in the urine chiefly in the case of the crystalline preparations; the fecal excretion was never more than 25 per cent of the total, usually 10 to 15 per cent.

Gold sodium thiomalate and gold sodium thiosulfate injected in amounts supplying equivalent amounts of gold result in similar plasma concentrations and excretion of gold. The plasma concentration and the excretion of gold vary with the size of the weekly dose but are usually not directly proportional to it. Except for the immediately higher blood gold values, intravenous administration of gold sodium thiosulfate gives results similar to the intramuscular injections.

When colloidal gold sulfide is administered, the plasma values and the excretion of gold vary in the different patients; most patients have low plasma gold concentrations and excrete but little gold even though colloidal gold sulfide is given in amounts providing much more gold than is supplied in the crystalline salts studied. These observations were clearly shown to be the result of quick phagocytosis of the gold particles getting into the circulation, and probably also the slower and less complete absorption from muscle or intestinal tract. The lower toxicity reported for this drug (and found by us) and our finding of much less frequent benefit seems inevitable in the light of these metabolic data.

Gold given as the sodium thiomalate or as sodium thiosulfate is retained in large amounts and is eliminated slowly. The amount of retention during treatment, the length of time gold is eliminated after administration correspond largely to the speed and amount of administration—the size of the weekly injection. Late toxic reactions were much more severe and frequent in patients receiving larger weekly injections of gold in a crystalline salt. Considering this fact in the light of the metabolism data, it would appear that many toxic reactions result from retention of gold in amounts sufficient to poison the patient and that such toxicity can be prevented by giving smaller doses of gold.

Gold is not concentrated in synovial fluid; it is present in joint fluid in an amount equivalent to, or less than, exists in plasma.

It is hoped that, with further pursuit of such investigations, gold therapy may be placed on a sound scientific basis and that, if its value is upheld, laboratory controlled methods of administration may be developed so that this therapy will become dependable and safe.

Bacteriostatic Action of Serum of Rheumatoid Arthritis Patients Treated with Gold Salts

DR. EDWARD F. HARTUNG, New York: Evidence is accumulating that the administration of gold salts will occasionally arrest the activity of rheumatoid arthritis. It is therefore natural to seek an explanation of the mode of action of this type of therapy. On the assumption that rheumatoid arthritis is a disorder of infectious etiology, I was interested to see if the blood was more or less bacteriostatic in vitro following the parenteral administration of various gold salts and colloidal preparations of gold. The bacteriostasis following administration of bismuth subsalicylate also was studied.

Since the hypothesized infectious agent of rheumatoid arthritis is unknown, other common laboratory organisms were used, most frequently a beta hemolytic streptococcus isolated from an acute mastoid infection. I do not feel, however, that the hemolytic streptococcus has been shown to be causally related to rheumatoid arthritis.

Related questions also were studied, such as the bacteriostasis of gold salts in vitro in varying dilutions and the determination of the agglutinin titers for hemolytic streptococcus before and after administration of gold salts.

The technic used in the determination of the bacteriostatic power of the serum was a slight modification of the method commonly used in this type of study. Measured amounts of culture were mixed with varying dilutions of serum, and after incubation the material was plated and colony counts made.

Subcutaneous injections of gold sodium thiomalate administered to rheumatoid arthritis patients in divided doses totaling as little as 60 mg. and up to 921 mg. were followed by a decided increase in the bacteriostatic power of the serum against the hemolytic streptococcus. The observed bacteriostatic effects were in rough proportion to the total amount of gold sodium thiomalate given, the maximum effect being attained after from 147 to 155 mg. had been administered. The bacteriostasis disappeared after stopping the administration for three to six months. The administration of gold sodium thiosulfate and "aurolsulfide" was also followed by a decided increase in the bacteriostatic power of the serum against the hemolytic streptococcus.

Parenteral injections of gold sodium thiomalate did not significantly increase or decrease the agglutinin titers for the hemolytic streptococcus. Colloidal gold in the amounts administered did not produce significant bacteriostasis. Bismuth subsalicylate was hardly more effective.

Gold sodium thiomalate was found to be bactericidal in vitro against a streptococcus hemolyticus in dilutions through 0.000001 per cent and bacteriostatic in higher dilutions. Other common laboratory organisms were similarly though not as strongly affected. The in vitro bacteriostasis was roughly proportional to the concentration of gold salt.

DISCUSSION ON GOLD THERAPY

DR. M. HENRY DAWSON, New York: Three or four years ago in discussing a paper I expressed the opinion that a therapeutic agent with such a degree of toxicity as gold should be used with the utmost caution; indeed, that perhaps its use was not justified at all. Since then the dangers of chrysotherapy have been reduced and it is now the general feeling among those who have had the most experience that gold salts constitute a valuable aid in the treatment of rheumatoid arthritis. Indeed, the value of gold salts is now so generally recognized that every effort is being made to develop less toxic compounds and to eliminate the unfavorable reactions. In studying the use of gold salts experimentally it is necessary to proceed indirectly because we do not yet know the cause of the disease. Therefore we have had papers dealing with gold salts in hemolytic streptococcus infections and in diseases due to pleuropneumonia-like organisms. Dr. Rothbard has stated that no favorable effect was observed in treating hemolytic streptococcus infections with gold sodium thiomalate after the disease was well established. This may well be due to the large amount of infecting culture employed. I believe that if small doses had been used a curative effect might well have been demonstrated. If Dr. Sabin's interesting results can be transferred to the clinic it would appear that he has made a significant contribution to the therapy of rheumatoid arthritis. However, I am sure that Dr. Sabin fully recognizes that many of the toxic reactions encountered with gold are hypersensitive in nature rather than heavy metal poisoning. Other means may have to be found to eliminate this type of reaction. In regard to calcium gold salts I believe there is one product available now, called myoral. I wonder if there is any information available concerning its toxicity or effectiveness? Dr. Sabin's calcium salt is now being tested out in several clinics and the reports will be eagerly awaited. It is interesting that Dr. Freyberg finds that gold continues to be excreted for eleven to thirteen months after the last injection. This is an important observation. I have observed 1 patient in whom nephrosis developed eleven months after the discontinuance of chrysotherapy. One cannot be sure that the nephrosis was due to the gold, but in view of Dr. Freyberg's report it would seem entirely possible. I have observed another patient who developed exfoliative dermatitis eight months after the last injection of gold. So one must be constantly on the watch for late toxic effects. I should like to ask whether the degree of bacteriostasis reported by Dr. Hartung is related to the amount of gold administered or to the blood level of the gold. Finally I should like to make one observation which is contrary to the findings reported by Dr. Hartung; namely, the effect of chrysotherapy on the hemo-

lytic streptococcus agglutination phenomenon. In my experience this reaction, once established in rheumatoid arthritis, rarely becomes negative. However, since the introduction of chrysotherapy I have noted a change in the capacity of the patients' serum to agglutinate hemolytic streptococci in a fair number of instances. This change has occurred in many cases which responded particularly well to treatment. The significance of this change remains to be evaluated. The reports this morning have all been concerned with laboratory investigations. It is obvious that continued clinical trial with gold salts is required before their value can be properly gaged. In the meantime I do not feel that it is a form of treatment which should be used by any but the most careful of physicians—preferably those who have had experience in its use.

DR. RUSSELL L. CECIL, New York: The impression prevails that experimental streptococcic arthritis is an acute pyogenic disease. It can be. It was produced by Dr. Rothbard with streptococci of all degrees of virulence. However, it can also be a progressive disease going on to chronic proliferative changes in the same way as the arthritis produced by the pleuropneumonia-like organism. Large doses of a highly virulent strain will always produce an acute arthritis. I do not know what Dr. Sabin means by progressive arthritis. Is it progressive for some time after the original inoculation? I see in experimental arthritis in rabbits and rats, the two animals with which I have chiefly worked, a streptococcic bacteremia after the injection, which sometimes persists for days or even several weeks, but one never gets new joint involvement in the animals after the bacteremia has disappeared. Streptococcic arthritis, while it is progressive so far as internal damage is concerned, is not progressive in the sense that new joints develop spontaneously. I would like to ask Dr. Sabin whether he can inform me on that point. Dr. Sabin spoke of a time and dose factor. That agrees with human experience. In studies with gold therapy on the human being I find that the results are better in the early cases than in the late ones. I also believe that there is a factor in dosage which is important; in other words, I like to give as large a dose as possible. I do not believe we can standardize our dosage in treating the human type of arthritis but I think we should give as much as is safe. With a big athlete I will feel more courageous than I would with a little spinster weighing 90 to 100 pounds. I wish I could believe that with 25 to 50 mg. once a week we are doing the patients as much good as with large doses. Unfortunately, from my experience that is not the case. Another point on which I have to digress a little from the speakers, and Dr. Freyberg particularly, is in the development of exfoliative dermatitis. In my experience exfoliative dermatitis has frequently come early in the disease while the dosage is still small, in other words, in highly susceptible people. If the patient gets over the first phase of gold therapy I feel comparatively safe.

DR. R. GARFIELD SNYDER, New York: It seems strange that of two university research departments the Cincinnati group says that it can cure 94 per cent of arthritis in mice if treatment is instituted within one week after the appearance of the first symptoms, while on the other hand the Cornell group says it was not able to obtain any cures after the arthritis was once established. The discrepancy of the results obtained as regards cures might be explained by the fact that the Cornell group does not state the time period which elapsed after the first appearance of the symptoms and the time it instituted treatment. Perhaps if it had started treatment within the first week its results would closely parallel Dr. Sabin's. Dr. Sabin brings up the question of instituting gold therapy within the first week after the appearance of symptoms. This should be tried out in a large series of cases to see if complete cures could not be obtained in a relatively large proportion of these cases. Dr. Freyberg's delicate and practical test for the presence of gold in the urine, feces and blood will probably be of great value in the future, because by using it extensively we may be able to develop a fairly accurate idea as to what is the minimum amount of gold we must have in the blood to be effective and also the maximum amount of gold a patient can tolerate in the blood without getting toxic symptoms. We have had two main objects in view at the Hospital for the Ruptured and Crippled: to see whether gold really is as effective as claimed and to see if by an excessive amount of care in its administration we could reduce the reported percentage of toxicity. While the current reports in Europe and this country in regard to toxicity range between 30 and 40 per cent, we succeeded in reducing our toxicity to 17 per cent. While European reports indicate 6 per cent serious toxic results, we have had only 3 per cent. An effort has been made to supply the medical profession with a gold preparation that is not toxic. The only one of this type on the market at the present time is Aurol-Sulfide. This salt has been used in several research clinics during the past year and a half, but the results to date are inconclusive. It is definitely less toxic than any other form of gold therapy, but unfortunately the clinical results obtained have not been very satisfactory up to the present time. Much more research must be done on the question of Aurol-Sulfide before any definite conclusions can be drawn with regard to the clinical value and effectiveness of this drug.

DR. J. ALBERT KEY, St. Louis: It is interesting that, with two types of disease, in one of them the gold cures the disease after it has started in experimental animals, and in the other it will prevent the development of the disease if given soon enough after the organisms are injected. How closely related these diseases are to rheumatoid arthritis we at present do not know. I agree with Dr. Cecil in emphasizing the fact that chronic arthritis is a disease in which the organism invades the joint and does a variable amount of damage and then invades other joints, but it does not move out of the first joint. When we speak of a cure of arthritis we must remember that the joint does not regenerate. If one is going to save the joint, it must be saved before the damage is done. Regarding the danger from gold, in the paper we presented four years ago we had 80 patients. We had four serious reactions with no deaths. Since that time we have had no serious reactions in the clinic. Dr. Rosenfeld had one serious case of purpura in a private patient who recovered. I do not give gold in my office, because I do not think a man should give gold unless he is willing to examine the blood and urine of his patients at frequent intervals. On the other hand, I think it is a safe drug to give. With a dose of 50 mg. of gold sodium thiomalate or 25 mg. of gold once a week the danger of serious reactions is decreased. I am interested to hear that Dr. Freyberg has shown that large doses of gold are not necessary for clinical results; in other words, if one can keep the gold in the plasma up to the optimal level, and that level will have to be determined by a lot of clinical observation followed by laboratory checks, that is all that is necessary. That will make the use of toxic material relatively safe. If nontoxic gold salts prove to be effective clinically, that will be a further boon. I wonder if Dr. Freyberg in his experimental animals found out where this gold that was retained was stored. I would expect it to be in the bone. In fact, it might be released by something that would lower the hydrogen ion concentration and might cause toxic symptoms later. I am much interested in the fact that gold has a bacteriostatic action similar to that of sulfanilamide and sulfathiazole. These also are toxic drugs and we use them. Clinically with gold we get a stasis of the disease more often than a cure; then the disease may recur. It seems to me that this bacteriostatic effect may point the way to the manner in which gold acts in the human being.

DR. CHARLES W. WAINWRIGHT, Baltimore: We have been using gold in Baltimore at the Johns Hopkins Hospital for the past year and a half. We have been convinced that gold is effective in bringing about a remission in chronic rheumatoid arthritis. The improvement noted has in our experience fallen into a pattern with sufficient regularity to take it beyond the realm of coincidence with spontaneous remission. Lessening of pain in the joint has been the first improvement noted, and objective changes have followed. With the first course of gold we have experienced a large percentage of minor toxic effects, as I think every one has who has used it. We have used only

gold sodium thiomalate and have started with small doses, increasing gradually to a dose of 100 mg., Dr. Freyberg's "conventional dose." We have not been able to determine blood levels and urinary and fecal excretion. However, our clinical impression has been that smaller amounts of gold are probably quite as effective as the larger ones, and if not as effective certainly much more safe. We have been rather disappointed in the fact that the use of gold has not seemed to influence at all the tendency of rheumatoid arthritis to relapse. Hence I speak of the ability of gold to bring about a remission in the disease. As a matter of fact, we have felt that probably the relapses occurred a little more often or sooner than those which followed a spontaneous remission. Of course it is highly desirable to know what is the optimum blood level and perhaps even to maintain it if it can be done without intoxication.

Dr. Charles L. Short, Boston: Rheumatoid arthritis is a difficult disease in which to evaluate therapy. There are spontaneous remissions even in cases that seem far advanced. My own experience has been small, but the cases I have treated have either been progressive or in a steady state for a year or more. I have treated 26, and of these, as far as I have followed them, I can really say that there has been definite therapeutic effect on only 4. I do not believe that this is more than one might get in the ordinary patient with rheumatoid arthritis under general treatment. I have used both gold sodium thiomalate and a compound called Neosolganol and have tried to give all these patients two full courses with the conventional doses. Over half of the patients suffered toxic reactions of one type or another, but fortunately only 1 has had a serious reaction—an exfoliative dermatitis. There have been 2 cases of severe herpes zoster, 1 involving the fifth nerve but fortunately not the eye. More carefully controlled clinical observations are needed before we can say that gold as used at present is of "undoubted value" in the treatment of rheumatoid arthritis.

Dr. H. M. Margolis, Pittsburgh: In the past few years my associates and I have used gold salts in the treatment of approximately 85 patients with rheumatoid arthritis. I do not think there is any question about the value of this drug when employed in conjunction with other necessary systemic measures in a well coordinated medical regimen. It is well not to underestimate the value of general systemic measures that are essential in addition to chrysotherapy. I have had the opportunity of observing patients who had been given injections of gold salts alone without much, if any, improvement. Yet these patients eventually got well when gold salts were used in conjunction with other general measures. That is not surprising, for a patient with painful, swollen joints who is undernourished, tired and anemic needs more than an injection of gold salts once a week. I am also convinced that patients treated in the early phases of the disease get better results than those treated late. Since some clinics still reserve gold therapy for the most advanced and refractory cases, reports of their results are apt to be more discouraging than if the drug had been administered in cases more amenable to such treatment. In evaluating the effectiveness of gold salt therapy in arthritis, it is well to note whether such patients had been given gold as a part of the initial therapeutic regimen or only after all other measures had been exhausted. It is to be remembered that gold salts appear to influence chiefly the exudative, periarticular changes; cartilage and bony changes are less amenable to the effect of this drug. In our first 50 patients we had approximately 40 per cent of mild reactions: mild pruritus, minor cutaneous reactions, stomatitis with aphthous ulcers in the mouth. Later we noted some of the more severe and more serious reactions. Two patients had severe leukopenia with reduction in the percentage of neutrophils. These developed during the early phases of their treatment with gold. They recovered when administration of gold was stopped. Had we not become aware of the neutropenia through weekly white cell counts checked before each injection, we might have induced a serious, and perhaps fatal, agranulocytosis. We have seen 2 cases of severe, generalized, eczematoid dermatitis apparently precipitated by gold. We have seen 2 cases of nephrosis characterized by severe albuminuria, without edema; otherwise, clinical evidence of renal irritation has been surprisingly absent. It seems that, if one treats enough patients with gold, one is bound to see reactions sooner or later. And small doses do not insure against reactions, even severe ones. The instance of most severe dermatitis and the only example of serious hepatitis occurred in patients who had had a little over 200 mg. of gold, given in small individual doses, distributed over a period of months. Consequently, I wonder whether the individual dose of gold, or the total amount administered, or the amount retained in the body plays much of a part in determining the incidence and severity of reactions. I have an impression that these reactions are conditioned more by idiosyncrasy than anything else.

Dr. William K. Ishmael, Oklahoma City: Could the beneficial effect from gold therapy in arthritis be the result of the damaging effect of this metal on the liver? In connection with Dr. Rothbard's report on the elevation of the nonprotein nitrogen in his cases, I have observed on several occasions that striking results were obtained when the patient had a "toxic" reaction from the gold therapy.

Dr. John W. Gray, Newark, N. J.: In the enthusiasm for the beneficial effects of gold salts we should not fail to emphasize its dangers repeatedly. Some physicians are afraid to give gold at all, while others give it in maximum doses without testing for idiosyncrasy and without repeated tests for toxicity. I have given gold treatment in nearly 200 cases, and about one-fifth of them showed sufficient evidence of toxicity for discontinuance of the drug. Renal complications occurred most frequently and, although the presence of casts in the urine is not as dramatic a reaction as the development of purpura, acute agranulocytosis or exfoliating dermatitis, it may prove to be just as serious unless the drug is discontinued when such evidence of renal irritation occurs.

Dr. Darrell C. Crain Jr., Washington, D. C.: I should like to ask what success has been achieved in preventing complications. I have started the rule of administering some vitamin K with gold salts on the empirical basis that it may stop the purpuric reactions. Although 35 patients is too small a number on which to judge, not one of them has had purpuric reactions. Two patients had rather severe cutaneous reactions which were controlled by large doses of vitamins B and C. They were given large doses of thiamine (usually 50 mg.) and 20 mg. of ascorbic acid and large doses of nicotinic acid (usually 250 mg.) all in one day, and both improved.

Dr. Currier McEwen, New York: In speaking of the hemolytic streptococcus agglutination reaction, Dr. Dawson mentioned that he has seen positive reactions change to negative as patients improved. I have noticed the same thing in a number of patients followed over a period of years. One of Dr. Hartung's slides showed a number of positive hemolytic streptococcus agglutination reactions with serums from normal individuals. In my experience I have never had a titer above 1 to 20 with normal serum, and even that low titer is extremely rare. I wonder, therefore, if some technical reason does not account for the lack of correlation shown in Dr. Hartung's slide.

Dr. Walter Bauer, Boston: Would Dr. Sabin describe the clinical course of untreated pleuropneumonia arthritis? Can Dr. Freyberg tell whether the injected gold can be mobilized by the methods commonly employed in the case of other heavy metals such as lead?

Dr. Cornelius H. Traeger, New York: I have used various types of gold therapy for the past six years and know its potential dangers. I want to caution against the indiscriminate use of gold therapy in early cases by those inexperienced in its use. Excessive enthusiasm for this drug in early cases must inevitably be followed by a wave of untoward reactions which might easily bring unmerited discredit to this type of therapy. This would be lamentable since it has a definite place in the therapeutic armamentarium of the physician treating arthritis. Only in the skilled hands of the physician who surrounds himself with all the proper safeguards is gold therapy in early

cases of arthritis advisable. Physicians unfamiliar with its use would do well to apply the more conservative measures which were used with some success before the advent of gold therapy. Until such time as newer and less toxic forms of gold are developed, let us be extremely cautious. I should like to take exception to one statement that was made: that continued therapy with gold increases the toxic results. That has not been my experience. I have used gold for nearly six years in hundreds of cases, and the longer I use it the less frequent are the toxic reactions.

DR. PHILIP S. HENCH, Rochester, Minn.: May I comment on Dr. Ishmael's question as to whether the effect of gold salts is produced via the liver? Among the 900 arthritis patients treated with gold by Hartfall, Garland and Goldie in 1937 almost 10 per cent (85) contracted jaundice presumably of the catarrhal type from toxic hepatitis. If so many patients had hepatitis to the point of actual jaundice one can only wonder how many others may have had a mild hepatitis insufficient to induce jaundice. It would appear, at least, that during chrysotherapy the liver is not uncommonly affected in varying degrees. Hartfall, Garland and Goldie noted no ameliorating effect of the "gold jaundice" on the arthritic symptoms, but unfortunately we do not know the exact intensity or character of the jaundice in their cases, as the concentration of bilirubin and the van den Bergh reactions were not reported. Those who attended the International Congress on Rheumatism and Hydrology in London in 1938 may recall that Dr. Schlesinger demonstrated at the Great Ormond Street Hospital a little boy who had had severe rheumatoid arthritis. He was given chysotherapy with excellent results so that without apparent pain or notable discomfort he ran around the room for us. In the discussion of this case it came out that the child had had severe gold hepatitis and jaundice, prior to which the effect of gold had not been striking but during which the child had rapidly and remarkably improved. Further evidence that the hepatitis and jaundice incident to chrysotherapy may invoke a dramatic remission of symptoms of rheumatoid arthritis is available. McFadzean of England wrote me about a woman with "acute rheumatoid arthritis" treated with gold. After three injections jaundice developed: "Within a week she had lost all the symptoms of rheumatoid arthritis and now six weeks after the onset of jaundice she is still absolutely free and doing the housework comfortably." Cecil recently (1940) reported that one of his patients who had "typical rheumatoid arthritis of four years' duration" developed toxic hepatitis with jaundice about eight weeks after the final (tenth) injection of sanocrysin. Prior to the onset of jaundice and despite the amount of treatment up to that time, she had considerable arthritis in various joints with swollen wrists and ankles, several fusiform fingers and swelling of the right knee. The jaundice lasted four to five weeks. "Within a week or so after the onset of jaundice, the swelling and pain disappeared entirely from her joints and there was complete restoration of function." This period of relief lasted three months; then her articular symptoms gradually returned. In most cases when gold is effective the results appear without jaundice and they appear gradually, not suddenly. In view of the more dramatic effect that may occur when actual gold hepatitis and jaundice occur, one wonders whether the liver may not be partly responsible also in those cases in which a less dramatic relief appears without jaundice. It has recently been reported that in normal animals gold is deposited in the parenchymal cells of many organs (especially the liver, spleen, kidneys and bone marrow), but in animals with chronic infections gold is deposited almost entirely in the cells of the reticuloendothelial system. We cannot state that chrysotherapy produces its effects by invoking the same phenomenon which occurs when spontaneous jaundice of various sorts relieves the symptoms of rheumatoid arthritis. But it would be of interest for investigators of chrysotherapy to study the effects of such therapy on the livers both of patients who are relieved and in those not relieved by injections of gold salts.

DR. SIDNEY ROTHBARD, New York: Dr. Dawson thought the amount of Streptococcus hemolyticus culture used to induce the arthritis in rats was too large and that because of this the gold would not cure the disease. This seems unlikely, since gold was effective in preventing the arthritis when rats were infected with similar amounts of culture. Moreover, the animals were not treated with the gold compound until seven days had elapsed after the onset of arthritis. At this time streptococci were not found in the blood stream or the synovial fluid of the involved joints. If smaller amounts than 0.5 cc. of culture are used, an insufficient number of animals develop the disease for curative experiments. Dr. Ishmael suggested that liver injury may explain why the rats with arthritis failed to respond to the gold therapy. Microscopic study of the livers of many of the experimental animals did not show any lesions other than a slight cloudy swelling of the hepatic cells. The third point raised was whether any studies had been performed to prevent the renal injury observed in these experiments. No investigations of this nature were made in our study.

DR. ALBERT B. SABIN, Cincinnati: The question raised by Dr. Dawson regarding the nature of toxicity of gold compounds has an important bearing on the relationship between the toxic manifestations observed in laboratory animals and those exhibited by human beings. It is our impression that our tests in laboratory animals measure only the "protoplasmic poison" effect of these compounds, while at least some of the toxic manifestations in man may be due to sensitization or other factors which are not reflected in determinations of the minimum lethal dose of a compound. Therefore, until we have some method of comparing the relative sensitizing capacities, if any, of various gold compounds in animals, we are limited in our experimental studies to determining whether one compound is more or less lethal than another, and only suitable clinical trial can indicate the effects of any compound in human beings. Dr. Cecil inquired as to what we meant when we used the word progressive with reference to the experimental arthritis, and Dr. Bauer asked me to say a little more about the clinical picture of the experimental disease. The experimental arthritis is produced by a single intravenous injection of the type B mouse pleuropneumonia micro-organism. Within twenty-four hours and thereafter the micro-organism can no longer be detected in the blood stream or in any of the viscera by suitable cultural methods. The available evidence indicates that this particular micro-organism has an affinity limited largely to the articular tissues, in which it appears to behave like an obligate intracellular parasite. Clinically the first signs of arthritis may begin as early as four to seven days after injection. The anterior and posterior extremities are equally affected, and fusiform swelling of isolated digits associated with involvement of the metacarpophalangeal or metatarsophalangeal joints is common. The joints are at first swollen and red but gradually lose this acute look and appear thickened and enlarged. The arthritis is migratory, new joints becoming involved while others recede. Thus the arthritis may disappear spontaneously from some of the joints, while in a certain number of others in the same animal it is progressive in that the joints continue to increase in size and after a variable period (two to six months) go on to deformity and ankylosis with associated atrophy of the neighboring muscles. It is of interest that new joints may become involved as late as five to six weeks after a single injection. Whether the organisms localize in all joints at once, the arthritis developing in them at different times, or whether there is a migration of organisms from affected joints to others in the body, we do not know except that cultures of the blood and viscera are regularly negative. The experimental disease is thus progressive in two respects: (1) the continued involvement of new joints over a period of weeks and (2) the continued activity of the pathologic process in some of the joints until ankylosis or deformity or both have supervened. Except for the arthritis, the mice appear to be in good health. The pathologic changes during the first week appear to be limited to the synovia, which undergoes proliferation, to the capsule, which exhibits a mild inflammatory reaction and proliferation of fibroblasts, and the joint space, which contains an increased amount of mucin and a slight cellular exudate consisting of almost equal numbers of polymorphonuclear and mononuclear

cells; during the second and third weeks there is evidence of beginning change in the cartilage with proliferation of the perichondrial cells, and at the end of four weeks in the joint with progressive arthritis one may already see a distorted articulating cartilage exhibiting necrosis in some areas and proliferation in others, with thickening of the synovia and capsule, in which foci of fibrinoid necrosis are present; at this time one also finds a proliferative reaction in the subchondral bone marrow and beginning obliteration of the free joint space. One may perhaps note some of the essential differences between this experimental disease and the streptococcic arthritis in rats described by Drs. Rothbard, Angevine and Cecil. The latter is for the most part not progressive and is self limited to such an extent that it would indeed be difficult to evaluate the possible curative effect of any compound on it. The essentially prophylactic effect of sodium aurothiomalate on the streptococcic arthritis is related to the bactericidal effect of gold on the streptococcus rather than to any effect on the established pathologic process. To be contrasted with this is the fact that sodium aurothiomalate has no demonstrable effect on the type B pleuropneumonia organism, the etiologic agent of the experimental disease in mice. As a matter of fact this micro-organism can be grown for several generations in the presence of therapeutically adequate amounts of gold and still produce arthritis. Whether or not the successful curative effect of this and other gold compounds on the fully developed arthritis in mice is due to an effect on the pathologic process or on the susceptible cells in which the etiologic agent has to multiply remains unknown. Dr. Key's remarks about the therapeutic effect of gold compounds in human arthritis occurring predominantly before extensive damage to the articulating cartilage has taken place is in agreement with our observations on the therapy of the experimental disease in mice. Dr. Wainwright's remarks regarding the relatively frequent occurrence of relapses that he and others have observed among patients treated with gold salts are of interest in relation to the effect of various doses of gold in the treatment of the experimental mouse arthritis. When doses of gold which are well above the minimal effective range are used, the arthritis disappears in nearly 100 per cent of mice and relapses are extremely rare. However, with doses in the minimal effective range (i e. a range in which the arthritis disappears in only 50 per cent of mice) or below it, the incidence of relapses may be higher than 50 per cent (i. e. the arthritis recurs spontaneously in animals in which it had completely disappeared). One may therefore perhaps be justified in wondering whether the dosage commonly used in human beings may not, from a therapeutic standpoint, be in the minimal or subminimal range.

DR. R. H. FREYBERG, Ann Arbor, Mich.: Whether the benefits attributed to gold salts are peculiar to gold or whether they may result from salts of other metals requires further study. It must be emphasized that calcium aurothiomalate has not yet been studied sufficiently in human beings to make any statement regarding its value in the treatment of rheumatoid arthritis. We recognize that the tissue concentration of gold may have more significance than the plasma concentration. However, it is difficult or impossible to measure the gold concentration in various human tissues. It can be measured in the blood. We are therefore trying to determine what value the plasma concentration has in guiding therapy. I feel that the nephrotoxic effects of gold preparations have not been sufficiently emphasized in the literature. We have seen some nephrotoxic effects and we are afraid of them. Dr. Dawson asked why we felt that the smaller doses of gold salts which result in a smaller retention of gold may be less harmful. In our experience to the present time all serious toxic reactions have occurred toward the end of therapy or after treatment had been stopped, and all occurred in patients who had received weekly injections of 100 mg. of gold sodium thiomalate or a comparable amount of gold. With smaller doses, although reactions occur, so far, no severe dermatitis or nephritis has been experienced. In the light of the metabolic data, showing that there is a greater retention of gold in persons to whom larger amounts of gold were given, should reactions occur in those patients, it is reasonable that they may be more severe and continue longer—for gold is present in the body in greater amounts and for a longer time. If as good therapeutic results can be obtained with small doses for these reasons, we feel that they should be used. In our experience thus far we have had as good results with smaller doses as with the larger, conventional doses. We have tested the cutaneous reaction to find out whether it would indicate persons who are "sensitive" to the drug. Such studies so far have been of no value. We hoped to learn whether differences in metabolism and excretion of gold accounted for (1) the therapeutic failures which occur all too frequently and (2) some or all toxic reactions to gold preparations. Such metabolic studies require a lot of time. The number of patients who can be studied thoroughly is comparatively small each year. To correlate toxic reactions and therapeutic effects with metabolic data in a sufficiently large group of patients in order to determine whether laboratory measures will control therapy will require more time. Dr. Key asked where gold is stored. We have studied a number of animals in an effort to answer this question. At present, final statement cannot be made. After fourteen daily injections of gold sodium thiomalate or gold sodium thiosulfate the kidneys contained the greatest amount of gold per gram of tissue, as far as the work has progressed. We have so far analyzed only the kidneys, heart, spleen, liver, the site of injection in muscles and the remainder of the carcass as a whole. We have not analyzed the bones or bone marrow separately. We have studies under way to find out whether gold is "stored" in the bone as other heavy metals are. I was glad that Dr. Wainwright emphasized that relapses occur after gold therapy. We have observed them after some of our best therapeutic results. I am also pleased that Dr. Short emphasized that not all patients are benefited by gold therapy. We have treated many who have shown no benefit. This perplexes me. Why are some patients benefited and others in apparently the same stage of the disease not? We hope we might answer that question by observation of the metabolism of gold to learn what different factors exist in different patients. I agree with Dr. Margolis that all gold can be expected to do is to check the inflammatory process. It certainly cannot rebuild damaged joints! I cannot answer Dr. Bauer's question as to how gold may be mobilized. That problem needs much more study. Little is known about the disease we are treating with gold preparations, and little was known about gold. We thought we could eliminate much or all of this second "unknown." If a certain minimum content of gold is necessary in the tissues to effect benefit, and if this amount is indicated by serum concentration or excretion studies, we should be able to learn this. Also if toxicity results from excesses of gold, serum or excretion studies should allow us to prevent such excesses. So it may be that laboratory methods may allow us to regulate gold therapy as potassium thiocyanate and sulfonamide drug therapy can now be regulated, making therapeutic effects more certain and toxic reactions less frequent and less severe.

DR. E. F. HARTUNG, New York: There are two questions I should like to answer, and I cannot answer either one satisfactorily. What is the correlation between gold levels on the serum of the blood and bacteriostasis? We started to use a method for quantitative analysis of gold and we soon found that it was applicable to urine but not to serum. It can be used quantitatively, but those quantitative results are not relative. In passing, I might say that our results on the analysis of gold in the urine are satisfactory. We got results similar to Dr. Freyberg's. I cannot state the correlation of gold in the urine with bacteriostasis. Bacteriostasis rapidly reaches the maximum after 60 or 80 mg. has been given and does not increase if a gram has been given. This bacteriostasis, when it becomes maximum, is not related to the interval between the last dose and the time the specimen is taken. Apparently from Dr. Freyberg's work the plasma levels are increasing or decreasing with each dose but the bacteriostasis is relatively constant because it appears at a relatively lower level of serum content of gold.

(To be continued)

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1931 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Orthopsychiatry, Menasha, Wis.

11:413-618 (July) 1941. **Partial Index**

Orthopsychiatry in the Community. P. L. Schroeder, Chicago.—p. 413.
Psychologic Factors Associated with Eating Difficulties in Children. Olga Rubinow Lurie, Chicago.—p. 452.
Obesity in Childhood and Personality Development. Hilde Bruch, New York.—p. 467.
Case Studies of Aggressive Delinquents. Ruth Topping, Warwick, N. Y. —p. 485.
Protection of Early Mental Growth: Some Social Implications in Present Crisis. A. Gesell, New Haven, Conn.—p. 498.
Early Home Background and Personality Adjustment. M. Marjorie Bolles, Harriet F. Metzger and Marjorie Wallace Pitts, New York.—p. 530.
Effect of Comic Books on Ideology of Children. Lauretta Bender and R. S. Lourie, New York.—p. 540.
National and International Difficulties: Suggested National Program for Alleviation. Margaret E. Fries, New York.—p. 562.

Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

46:145-286 (Aug.) 1941

*Polyostotic Fibrous Dysplasia. K. Kornblum, Philadelphia.—p. 145.
Leptomeningeal Cysts: Roentgenologic Viewpoint. C. W. Schwartz, New York.—p. 160.
Reversible Bronchiectasis. F. G. Fleischner, Boston.—p. 166.
Spontaneous Renal and Perirenal Emphysema: Report of Case in Diabetic from Escherichia Coli Infection. C. L. Gillies and R. Flocks, Iowa City.—p. 173.
Roentgenologic Consideration of Influenzal Pneumonitis. A. J. Ackermann, Oklahoma City.—p. 175.
Primary Lymphosarcoma of Jejunum. S. Shulman, Far Rockaway, N. Y.—p. 182.
Appearance and Nature of Cystlike Areas in Distal Femoral Metaphyses of Children. L. W. Sontag and S. I. Pyle, Yellow Springs, Ohio.—p. 185.
Roentgenologic Examination of Soft Tissues: I. Technical Considerations; II. Study of Axillary Region. Georgette J. Melot, Brussels, Belgium.—p. 189.
Deformities and Fractures of Vertebrae as Result of Senile and Presenile Osteoporosis. L. Nathanson and A. Lewitan, Brooklyn.—p. 197.
Vertebra Plana (Calvé): Report of Two Cases. F. Y. Kuhlman, Fort Arthur, Texas.—p. 203.
Radiation Treatment of Cancer of Rectum: Technic for Radium Needles Through Perineal Stab Wounds. G. S. Sharp, Pasadena, Calif.—p. 207.
Radiation Treatment of Hemangioma. J. Spencer, Portland, Maine.—p. 220.
Hyperparathyroidism: Its Treatment with Roentgen Irradiation. S. Rubenfeld, New York.—p. 224.
Carcinoma of Penis. L. H. Jorstad, St. Louis.—p. 232.
Attempt to Correct Asymmetry in Leg Length by Roentgen Irradiation: Preliminary Report. W. S. Judy, Greenville, S. C.—p. 237.
Roentgenologic Report of Chest Examinations. H. E. Ashbury, Baltimore.—p. 241.

Polyostotic Fibrous Dysplasia.—Kornblum reports 2 cases of polyostotic dysplasia which emphasize that, although its diagnosis can be suspected from the clinical and roentgen manifestations, confirmation depends on microscopic study of bone. The disease is primarily one of childhood, but because of the protracted course the condition is not encountered until adolescence or adult life. Pain, limp and deformity of one lower extremity are the usual clinical features. The onset of symptoms is insidious; pain and disability are slowly progressive, and deformity usually becomes manifest at the height of the disease during adolescence or early adult life. The disease is apparently never fatal and never cured. It becomes less active with increasing age. The most striking feature of it is the rather typical roentgen appearance of osteitis fibrosa. Apparently no bones are exempt, although those of the lower extremities are more frequently affected. With an increase in the size of the lesions there is a thinning of the cortex of the bone, which eventually may expand slightly. Functional activity of the weakened bones causes deformities to develop. Loss of bone substance and thinning of the cortex predispose to pathologic fractures. With increasing age the lesions tend to retard but never actually disappear. In polyostotic fibrous dysplasia the serum calcium level may be normal or even slightly elevated but never as high as in hyperparathyroidism. There is no significant change in the serum phosphorus. The phosphatase content of the blood is moderately increased. Patients on low calcium diets excrete normal amounts of calcium in the urine. Positive differentiation from hyperparathyroidism depends on the microscopic study of bone, in which the following should be observed: a thinning of the cortex, a replacement of the marrow and spongiosa by dense, gritty, rubbery fibrous tissue interspersed with poorly calcified bone spicules and an absence of cyst formation. An exploratory operation for a parathyroid tumor is not justified until the clinical, roentgen, chemical and microscopic features of the disease have been investigated thoroughly and found lacking.

Archives of Pathology, Chicago

32:315-506 (Sept.) 1941

Calcification and Ossification: Mobilization of Bone Salt by Parathyroid Extract. F. C. McLean and W. Blood, Chicago.—p. 315.
Tissue Reactions in Fatal Cases of Streptococcus Hemolyticus Infection. G. K. Mallory and C. S. Keefer, Boston.—p. 334.
"Corrected Transposition" and Persistent Rudimentary "Right Aorta" as Evidence in Support of Spitzer's Theory. A. A. Liebow and W. McFarland, Meriden, Conn.—p. 356.
Experimental Lesions Produced by Cerebrosides. O. O. Christianson, University, Ala.—p. 369.
Sickle Cell Disease: Two Cases, One Presenting Fat Embolism as Fatal Complication. B. M. Vance and R. C. Fisher, New York.—p. 378.
Experimental Rickets: Blood and Tissue Changes in Puppies Receiving Diet Very Low in Phosphorus, With and Without Vitamin D. S. Freeman and F. C. McLean, Chicago.—p. 387.
Insufficiency of Aortic Valve Due to Syphilis: Study of Its Genesis. R. S. Jason, Washington, D. C.—p. 409.
Chemical Studies of Susceptibility to Spontaneous Carcinoma of Mammary Gland in Mice: II. Indications for Analysis of Genetic Factor of Susceptibility in Relation to Nongenetic Influences. L. C. Strong, New Haven, Conn.—p. 420.
Improved Method for Experimental Grafting of Skin. D. E. Barker, Cincinnati.—p. 425.
Adrenal Cortex. E. C. Kendall, Rochester, Minn.—p. 474.

Archives of Surgery, Chicago

43:327-540 (Sept.) 1941

*Studies on Experimental Hypertension. H. Goldblatt, J. R. Kahn, Cleveland, and H. A. Lewis, Los Angeles.—p. 327.
*Naevus Unius Lateris. G. T. Pack and D. A. Sunderland, New York.—p. 341.
Histologic Distribution of Vitamin in Biopsy Specimens of Liver. K. A. Meyer, H. Popper and A. B. Ragins, Chicago.—p. 376.
*Hyperthyroidism and Adenocarcinoma of Thyroid Gland. M. T. Friedell, Rochester, Minn.—p. 386.
Inguinal Ectopia of Ovary and Fallopian Tube: Review of Literature and Report of Case of Infant. V. Mayer, Brooklyn, and F. G. Templeton, Warren, Pa.—p. 397.
Gynecologic Mortality. R. L. Faulkner, Cleveland.—p. 409.
Treatment of Intussusception. J. Ireland, Chicago.—p. 418.
Relation of Splenic Extract to Etiology of Essential Thrombopenia. M. L. Colmer and W. L. Mersheimer, New York.—p. 422.
Nerves in Vertebral Canal: Their Relation to Sympathetic Innervation of Upper Extremities. C. Van Buskirk, St. Louis.—p. 427.
Trichomonas Infection of Male Genitourinary Tract. C. Baumeister, Los Angeles, and Nell Hollinger, San Jose, Calif.—p. 433.
Mediastinal Emphysema and Bilateral Pneumothorax Following Radical Dissection of Neck. L. V. Ackerman and E. M. Bricker, Columbia, Mo.—p. 445.
Stored Dextrose-Citrate Plasma in Treatment of Operative Shock. E. L. Besser, Iowa City.—p. 451.
Foreign Bodies in Biliary Tract: Report of Case with Tabular Review of Literature. F. H. Bowen, Jacksonville, Fla.—p. 458.
Venous Thrombosis: Early Diagnosis with Aid of Phlebography and Abortive Treatment with Heparin. G. Bauer, Mariestad, Sweden.—p. 462.
Congenital Lumbosacral Defect. J. G. Sinclair, N. Duren and J. C. Rude, Galveston, Texas.—p. 473.

Experimental Hypertension.—Goldblatt and his associates report experiments on dogs which may prove of value in solving the clinical problem of whether unilateral nephrectomy should be performed in order to lower the blood pressure in some clinical cases of hypertension in which one kidney is obviously diseased and probably ischemic. On the basis of their data they say that lowering of the blood pressure should not be expected to follow excision of a completely nonfunctioning

kidney whose lack of function is due to occlusion of the ureter, even though clinically there is some indication that such a kidney may still be responsible for the hypertensive effect. Under such circumstances, at least for the present, it is probably best to perform nephrectomy only if the obviously diseased kidney is the source of other untoward clinical effects (infection or persistent pain) for which removal might in any event be indicated. Nephrectomy should be done mainly to remove the diseased organ rather than for the possible cure of the hypertension. In contemplating unilateral nephrectomy it is desirable to determine as far as possible that the other kidney is normal, before the obviously diseased, though still functioning, kidney is removed for the possible favorable effect that the procedure may have on the elevated blood pressure.

Unilateral Nevus.—According to Pack and Sunderland, only 4 cases of neuropathic papilloma or naevus unius lateris were observed among 40,000 patients with neoplasms studied at the Memorial Hospital. With the 156 reported in the literature, these make 160. The peculiar linear unilateral distribution is not limited to nevi of the verrucous or papillary type, and the nevus may involve any of the components of the skin. The authors believe that such nevi form a clinical entity sufficiently characteristic to deserve individual classification. Lesions of the trunk are usually arranged in a transverse manner and those of the extremities in longitudinal or spiral streaks. However, there is no one characteristic pattern of distribution. Only one third of the tumors show any relation to nerve distribution. Rarely is there any evidence of a hereditary factor. Almost half of the lesions appear at or shortly after birth and most of the remainder in early life. More than two thirds of the nevi are pigmented. Microscopic examination reveals chiefly hyperkeratosis, distorted epidermis and elongated papillas. Subjective symptoms, if they occur, are itching or irritation. Many forms of treatment have been employed, with varying degrees of success. The authors believe that surgical excision of the entire thickness of the involved epidermis is the method of choice. The cause of the condition remains unknown, but the trophic influence of nerves cannot be excluded as a pathogenic factor. The pathologic process appears to be located solely in the epidermis. The occurrence of various congenital skeletal malformations and nervous disorders appear to be more frequent in persons with naevus unius lateris than in those unaffected, but the possibility of mere coincidence cannot be discarded. Three of the authors' 4 patients died of cancer, in 1 multiple basal cell carcinomas developed in the nevus (the axillary nodes were involved by epidermoid carcinoma, presumably metastatic from some undetected primary epidermoid cancer in the papillary nevus, this patient dying of pulmonary metastases), 1 patient died at the age of 23 from pulmonary metastases of carcinoma of the breast which had been covered with nevi and heavily irradiated and 1 patient died of carcinoma of the esophagus and stomach at the age of 43. However, in this patient there is little basis on which to assume more than coincidental occurrence of the nevus and the carcinoma.

Hyperthyroidism and Adenocarcinoma of Thyroid.—Friedell discusses the association of hyperthyroidism with primary adenocarcinoma of the thyroid in which not only clinical variations but the coincidental presence of other benign pathologic changes in the thyroid are involved. From 1917 through 1937 there were at the Mayo Clinic 412 microscopically proved and graded (Broders' method) adenocarcinomas (primary malignant neoplasms of epithelial origin) of the thyroid. Each of the tumors was considered an adenocarcinoma despite scirrhous, papillary or malignant adenoma variations. A clinical diagnosis of hyperthyroidism was made in 57, or 13.8 per cent, of the 412 cases. All the patients were operated on. Hyperthyroidism was much more frequently associated with the lower than with the higher malignant grades of adenocarcinoma. Although a definite conclusion that adenocarcinoma of the thyroid is the source of functional hyperactivity cannot be drawn, evidence points to the possibility that the adenocarcinoma, like adenocarcinoma of other endocrine glands, at times and in part may perform the functional role of benign thyroid tissue. The inverse relation between the increase in malignant grade and decrease in hyperthyroid frequency seems especially significant. Another close relation of adenocarcinoma to hyperthyroidism is the presence of multiple adenomas. As the malignant grade advances the frequency of multiple adenomas decreases, but about half of the adenocarcinomas (of any grade) associated with hyperthyroidism occur in thyroids containing multiple adenomas. In most cases the benign gross and microscopic changes in the thyroid will quickly eliminate the adenocarcinoma as the only possible source of thyrotoxicosis. The hypothesis that an anaplastic tumor should retain less of the normal function of its constituent cells as the degree of anaplasia advances is an attractive one and has been voiced by Ewing. Function may be a property of adenocarcinoma of the thyroid and hyperthyroidism an adjunct of it.

Arkansas Medical Society Journal, Fort Smith

38:61-78 (Aug.) 1941

Vaccine for Epidemic Influenza: Preliminary Report. F. M. Acree, Greenville, Miss.—p. 61.
Pain and the Menstrual Cycle. J. H. Sanderlin, Little Rock.—p. 64.

Bulletin New York Academy of Medicine, New York

17:567-648 (Aug.) 1941

Puerperal Infection: Consideration of Relationship of Pathologic Changes and Bacteriologic Findings to Prevention and Treatment. W. E. Studdiford, New York.—p. 567.
*Brucellosis. W. M. Simpson, Dayton, Ohio.—p. 592.
Dental Foci of Infection. C. G. Darlington, New York.—p. 618.
Lymphogranuloma Venereum. A. W. Grace, New York.—p. 627.

17:649-734 (Sept.) 1941

Surgical and Nonsurgical Treatment of Prostate Gland. O. S. Lowsley, New York.—p. 651.
Infections of Mouth, Pharynx and Upper Respiratory Tract. J. D. Kernan, New York.—p. 674.
The Doctor in Court. B. L. Shientag, New York.—p. 692.
Id. G. Z. Medalie, New York.—p. 697.
Id. C. G. Heyd, New York.—p. 706.

Brucellosis.—Simpson has seen 220 patients with brucellosis. Ingestion of raw milk or unpasteurized dairy products was the source of infection and only 24 of the infections have occurred since 1931, when the universal pasteurization ordinance was passed. Each of the 24 patients was known to have consumed raw milk or its products elsewhere. Brucellosis, because it presents many symptoms and signs common to typhoid, malaria, tuberculosis and influenza, is frequently confused with these diseases. Less often the disease has been confused with acute rheumatic fever, subacute bacterial endocarditis, bronchitis, pyelitis, appendicitis, cholecystitis or tularemia. The symptoms of acute and chronic brucellosis vary greatly. The chronic ambulatory form is widely prevalent, is often confused with other diseases and is frequently not recognized. Many neurasthenic persons and patients with fever of unknown cause have been found to be victims of chronic brucellosis. Less than 10 per cent of patients with chronic brucellosis have had a previous acute febrile illness compatible with a diagnosis of acute brucellosis, which is initiated by a sharp chill and rapid elevation of temperature, often followed by a few or all of the following symptoms: tiredness, weakness, loss of appetite, constipation, headache, backache, cough, arthralgia, muscular pains, restlessness, insomnia and signs of encephalitis, myelitis or meningitis, and sometimes, in the severe instances, of vegetative endocarditis. The only procedure by which the diagnosis of brucellosis may be established is the cultivation and identification of the Brucella organism. Agglutination and cutaneous tests are of value in the diagnosis of acute brucellosis, but they are inadequate for the diagnosis of the chronic form. The opsonocytophagic test has also yielded inconsistent results. The test proved to be of little or no value as a diagnostic procedure or a therapeutic guide. Brucella vaccine therapy has produced favorable results in from 60 to 85 per cent of patients with acute or chronic brucellosis. Sulfanilamide and its derivatives are apparently of little value. Artificial fever therapy is particularly efficacious in patients who do not respond to vaccine therapy. The mortality rate is about 2 per cent. During 1936 there were 107 official reports of deaths from brucellosis in the United States. The mortality is not a true criterion of the importance of the disease. The prolonged course and the resulting chronic ill health make it a much more serious disease than the death rate indicates. Prophylaxis, that is, pasteurization

of milk and dairy products and the elimination of the disease in cattle, is the most important control measure. The campaign engaged in by the United States Department of Agriculture to eradicate brucellosis in cattle should extend to the control of the disease in hogs and goats.

California and Western Medicine, San Francisco

55:55-112 (Aug.) 1941

Problems of Adrenal Insufficiency. R. F. Loeb, New York.—p. 61.
Surgical Lesions of Adrenal Glands. W. Walters, Rochester, Minn.—p. 64.
Medical Preparedness in California. P. K. Gilman, San Francisco.—p. 68.
Needs of the Medical Department of the Navy. E. U. Reed, San Francisco.—p. 70.
Aviation Medicine. R. G. Davis, Mare Island.—p. 71.
Needs of the Medical Corps of the Army. J. H. Schaefer, San Francisco.—p. 74.
Necessity of Yardstick in Selective Service Examinations. B. S. Thomas, Sacramento.—p. 75.
Stretching Test in Neuritis. R. Wartenberg, San Francisco.—p. 76.
Postgraduate Education in Obstetrics. W. B. Thompson, Los Angeles.—p. 79.
Cutaneous and Mucous Membrane Cancer. H. J. Templeton, Oakland.—p. 81.
Neoplasms of Reticuloendothelial Tissues. J. W. Budd, Los Angeles.—p. 84.
Regional Anesthesia with Intracain. C. F. McCuskey, Glendale.—p. 86.
William Hunter's Lectures of 1775: Two Rare San Francisco Manuscripts. J. M. D. Olmsted, Berkeley.—p. 87.
Beautification and Irrigation of Golden Gate Park with Clarified, Disinfected Sewage Effluent. J. C. Geiger, San Francisco.—p. 89.
Medical History Repeats Itself. H. E. Thelander, San Francisco.—p. 91.

Canadian Public Health Journal, Toronto

32:387-434 (Aug.) 1941

The Health of the Nation. C. E. Dolman, Vancouver, B. C.—p. 387.
Occurrence of Diphtheria in Halifax from Oct. 1, 1940 to Jan. 31, 1941. P. S. Campbell, Halifax, N. S.—p. 404.
*Convalescent Serum in Treatment of Poliomyelitis. N. Silverthorne, W. A. Hawke and A. Brown, Toronto.—p. 410.
Schick Test in Adults. G. D. W. Cameron, Ottawa, Ont.—p. 412.

Convalescent Serum for Poliomyelitis.—Silverthorne and his associates studied the efficacy of serum therapy in the course of the epidemic of poliomyelitis in Toronto in 1937. The study, begun after the peak of the epidemic, extended over six weeks. The patients were free from paralysis when serum was given. Forty-five alternate patients were and 47 were not given 50 cc. of convalescent pooled serum from paralytic patients infected years before. There was no significant difference between the two groups as to the time the treatment was given and the duration of symptoms. There was a slight but probably not significant difference among the severely paralyzed patients: 22 per cent in those given serum compared with 8.5 per cent in the controlled group. In the treated group there were 7 patients with slight, 5 with moderate and 1 with severe paralysis; the respective figures for the control group were 6, 4 and 4. The results of the study would suggest that serum in the doses given did not prevent paralysis.

Cancer Research, Baltimore

1:517-594 (July) 1941

Inheritance of Retinoblastoma and Its Relationship to Practical Eugenics. C. V. Weiler, Ann Arbor, Mich.—p. 517.
Early Cancer of Stomach: Study of 1,299 Resected Ulcers and 2,408 Cancers. W. C. MacCarty Sr., Rochester, Minn.—p. 536.
Malignant Melanoma Cutis. S. Peller, New York.—p. 538.
Antigenic Nature of Purified Chicken Tumor Agent: Preliminary Report. M. K. Barrett, New York.—p. 543.
Growth of Brown-Pearce Carcinoma in Anterior Chamber of Eyes of Tumor-Immune Rabbits. O. Saphir, M. Appel and A. A. Strauss, Chicago.—p. 545.
Cellular Injury in Relation to Proliferative and Neoplastic Response. V. Menkin, Boston.—p. 548.
Resistance of Tumor Cells in Tissue Culture to Growth-Inhibiting Action of Amines. A. M. Brues and Elizabeth B. Jackson, Boston.—p. 557.
Induction of Leukemia in Mice Following Percutaneous Application of 9,10-Dimethyl-1,2-Benzanthracene. L. W. Law, Bar Harbor, Maine.—p. 564.
Genetic Analysis of Induction of Tumors by Methylcholanthrene: II. Influence of Spindle Cell Sarcoma and of Carcinoma of Skin on Each Other. L. C. Strong, New Haven, Conn.—p. 572.
Sex Difference in Conjunctive Tumoral Reaction of Guinea Pig Toward Natural and Artificial Estrogens. A. Lipschütz, L. Vargas Jr. and J. Palma, Santiago, Chile, South America.—p. 575.

Endocrinology, Springfield, Ill.

29:1-164 (July) 1941. **Partial Index**

Effect of Increasing Number of Daily Injections of Gonadotropic Preparations on Ovaries of Immature Rats. R. K. Meyer and W. H. McShan, Madison, Wis.—p. 31.
Antihormone Production to Crude and Purified Pregnant Mare Serum Preparations. A. S. Gordon, New York.—p. 35.
Vaginal Estrus in Irradiated Mice. S. H. Geist, J. A. Gaines and G. C. Escher, New York.—p. 59.
Absorption of Pellets of Crystalline Testosterone, Testosterone Propionate, Methyl Testosterone, Progesterone, Desoxycorticosterone and Stilbestrol Implanted in the Rat. T. R. Forbes, Baltimore.—p. 70.
Effect of Testosterone Propionate on Reproduction in the Female. J. W. Huffman, Chicago.—p. 77.
Beneficial Action of Testosterone in Experimental Renal Atrophy Caused by Ligature of the Ureter. H. Selye and S. M. Friedman, Montreal, Canada.—p. 80.
Radioactive Iodine as Indicator in Thyroid Physiology: III. Iodine Collection as Criterion of Thyroid Function in Rabbits Injected with Thyrotropic Hormone. S. Hertz and A. Roberts, Cambridge, Mass.—p. 82.
Effect of Testosterone Propionate on Creatinuria of Experimental Hyperthyroidism in Male and Female Monkeys. J. W. Jailer, New York.—p. 89.
Effect of Administering Thyrotropic Hormone With and Without Iodine on Thyroid Tissue Metabolism. J. E. Vanderlaan, W. R. Vanderlaan and M. A. Logan, Boston.—p. 93.
Thyroid-Ovarian Relations: I. Influence of Ovarian Hormones on Thyroid Hyperplasia. L. A. Emge and Gert L. Laquer, San Francisco.—p. 96.
Refractoriness Produced by Sodium Retaining Substances. F. A. Hartman and Lena A. Lewis, Columbus, Ohio.—p. 111.
Sodium Chloride and Dextrose Appetite of Untreated and Treated Adrenalectomized Rats. C. P. Richter, with assistance of G. H. Bunch Jr. and H. E. Wooden Jr., Baltimore.—p. 115.
Influence of Fever on Vagoinsulin and Sympatheticoadrenal Systems. J. Feldman and E. Gellhorn, Chicago.—p. 141.
Effects of Desoxycorticosterone Acetate in Albino Rat. W. H. Carnes, C. Ragan, J. W. Ferrebee and J. O'Neill, New York.—p. 144.
Interpretation of Thymus Bodies. B. F. Kingsbury, Ithaca, N. Y.—p. 155.

New England Journal of Medicine, Boston

225:247-278 (Aug. 14) 1941

Potentialities of Preventive Geriatrics. E. J. Stieglitz, Bethesda, Md.—p. 247.
Certain Observations in Low Nitrogen, Normal Oxygen Atmospheres Related to Problems of High Altitude Flying. A. M. Butler, J. L. Wilson, C. A. Smith and S. Farber, Boston.—p. 255.
*Chronic Gastritis: Gastroscopic and Clinical Study. C. W. McClure, F. N. Sweetsir and I. R. Jankelson, Boston.—p. 259.
*Recent Developments in Aviation Medicine. J. F. Fulton, New Haven, Conn.—p. 263.

225:279-316 (Aug. 21) 1941

Standard Electroencephalographic Technic for Localization of Gross Intracranial Lesions. F. A. Gibbs, D. Munro and W. R. Wegner, Boston.—p. 279.
Temporal Arteritis. L. H. Hoyt, G. A. Perera and A. J. Kauvar, Boston.—p. 283.
Electrocardiographic Findings Associated with Gunshot Wound of Heart: Report of Case. W. A. Fraser and M. Texon, New York.—p. 286.
Treatment of Dehydration in Patients with Hypertrophy of Prostate, Retention of Urine and Impairment of Renal Function. F. A. Simeone, Boston.—p. 299.

Chronic Gastritis.—McClure and his associates determined the frequency of chronic gastritis observed at the gastroscopic examination of 611 consecutive patients. Gastritis was present in 269; 150 had the hypertrophic, 51 the atrophic and 68 the superficial type of the disease. To evaluate the symptoms of chronic gastritis, 75 patients were subjected to comprehensive studies. Changes in weight and constipation were not of great clinical importance. Men had more frequently the hypertrophic and women the atrophic type of gastritis. In general the age incidences and the duration of the symptoms for the two types of gastritis were comparable, indicating that gastritis was a chronic condition. Of 68 patients showing hypertrophic or atrophic gastritis, 20 had a duodenal ulcer, 1 had a gastric ulcer and 6 presented roentgen evidence of disease of the gallbladder or had had a cholecystectomy. The presence of gastric ulcer was verified by gastroscopic observation. The condition of the remaining 41 patients was not complicated; 30 complained of epigastric discomfort or mild pain and 9 of severe epigastric pains. The pains were invariably related to the time of food taking and were invariably relieved by the ingestion of food or alkali. Of the 2 patients with atrophic gastritis without pain or discomfort, 1 complained of nausea and fatigue and 1 of fatigue and regurgitation of small amounts of bloody liquid. A

third of the patients with the atrophic type of gastritis complained of fatigue. It was absent in the hypertrophic group. The correlated data show that except for fatigability and absence of epigastric complaint in 2 patients with atrophic gastritis the symptoms of hypertrophic and atrophic gastritis are similar. Ten of the 75 patients had symptoms characteristic of peptic ulcer. Roentgen observations were of inconsequential value as a direct aid in the diagnosis of gastritis. However, barium gastrointestinal studies were of value in determining the presence or absence of esophageal lesions, cancer, ulcer of the stomach, pyloric obstruction, duodenal ulcer and lesions elsewhere in the small or large intestine.

Aviation Medicine.—Fulton summarizes the recent literature on aviation medicine. The limitations of air combat rest more with the pilot than with the plane, and the government that succeeds in adequately protecting the pilot through study of his physiologic needs will have a decisive strategic advantage in combat. Modern combat flying, especially the dive bombing maneuver, causes the development of centrifugal forces along the longitudinal axis of the body drawing blood away from the head and causing collapse from acute cerebral anoxia. A healthy young adult can withstand a positive acceleration along the vertical axis of the body of 4.5 g (four and a half times the force of gravity) for approximately five seconds. But from the point of view of safety in aviation the pilot's coordination prior to loss of consciousness is vital. The condition of the organism determines the capacity to withstand acceleration; an alcoholic spree and an empty stomach diminish it. The German literature also states that the following favor the pilot's capacity: inhalation of 5 or 6 per cent carbon dioxide, vasoconstrictor drugs, increase in the tone of the capillary wall, posture and mechanical constriction of the abdomen and of the lower extremities by pneumatic belts and trousers. The Germans favor a crouching position, with the legs flexed against the abdomen. All factors that tend to improve the body's resistance to positive acceleration are those that keep blood in the head. Recently the use of oxygen in low altitude ranges has become an established practice to avert impairment in mental functions as it has among high altitude squadrons for the sake of washing out nitrogen. For the breathing of oxygen an ideal face mask is yet to be found. For supplying oxygen the new aluminum alloy tanks weigh much less than the old tanks but they are more vulnerable to machine gun penetration and are probably a greater hazard to the pilot and the ship than the heavy tanks. Pressure cabin planes have not proved feasible for light combat aircraft. The experiencing by high altitude pilots of symptoms similar to those of bends not attributable to anoxia, acceleration or metabolic disturbance has been thought to be due to sudden pulmonary air embolism. Direct proof that high altitude bends are caused by the liberation of nitrogen has not been established, but the similar symptoms make indirect evidence highly impressive. Tests in decompression chambers suggest that at least 50 per cent of young male adults can withstand altitudes up to 40,000 feet for from one to six hours without bends developing. Hence high altitude squadrons should be selected on the basis of these tests. The replacing of nitrogen with helium or by preoxygenation is not feasible, but with the delaying effects of pure oxygen from the ground up bends may cease to be a serious problem in military aviation. Regarding anoxia of the adrenals, it is not yet clear whether the administration of adrenal cortex extract would facilitate the pilot's adjustment to high altitudes or improve his performance.

Northwest Medicine, Seattle

40:265-308 (Aug.) 1941

Cerebral Birth Injury. M. G. Peterman, Milwaukee.—p. 267.
Glucose-Insulin Treatment in Hyperemesis Gravidarum. D. F. Bice, Yakima, Wash.—p. 270.
Practical and Inexpensive Plasma Bank. L. J. Rosellini, Mildred Porter and C. R. Jensen, Seattle.—p. 272.
Total Gastrectomy for Diffuse Superficial Carcinoma. J. W. Baker, Seattle.—p. 277.
Curare and Scopolamine in Convulsive Therapy. R. J. Bennett, Fort Steilacoom, Wash.—p. 280.
Meningococcic Septicemia: Prolonged Case Treated with Three Sulfonamide Drugs. Marian G. Hayes, Eugene, Ore.—p. 284.
Bone Tumor: Problem of Diagnosis. C. G. Bain, Chehalis, Wash.—p. 287.

Ohio State Medical Journal, Columbus

37:725-820 (Aug.) 1941

Diet, Health and Defense. C. A. Elvehjem, Madison, Wis.—p. 741.
Method for Instilling Iodized Oil in Trachea for X-Rays. J. R. Jarvis, Van Wert.—p. 746.
Previous Uterine Infection as Predisposing Cause for Spontaneous Rupture of Uterus. J. G. Fleming, Cincinnati.—p. 747.
Thrombosis and Embolism of Abdominal Aorta: Report of Case with Obstruction of Renal Arteries. M. L. Siegel and C. F. Garvin, Cleveland.—p. 750.
Chills and Fever as Manifestation of Sulfathiazole Toxicity. W. E. Molle and W. Buck, Cincinnati.—p. 752.
Acute Suppurative Nephritis Following Hysterectomy: Case Report. E. Eichner, Cleveland.—p. 754.
Clinical Aspects of Malignancy of Lung: Case Reports. O. Berghausen, Cincinnati.—p. 757.
Craniocerebral Injuries. J. N. Wychgel and W. J. Urbanski, Cleveland. —p. 761.
Thoracentesis of Chest—Inexpensive Method. A. A. Roth, Cleveland.—p. 764.
Surgical Relief of Intractable Pain in Upper Extremity Due to Malignant Disease. L. M. Weinberger, Chicago.—p. 765.
Specific Therapy in Coseasonal Management of Hay Fever: Importance of Controlled Variation of Dosage. L. E. Seyler, Dayton.—p. 768.
Unilateral Exophthalmos and Spinal Cord Compression in Case of Multpile Myeloma. J. Flynn and S. Sailer, Cincinnati.—p. 771.

Public Health Reports, Washington, D. C.

56:1581-1636 (Aug. 8) 1941

Skin Hazards in Airplane Manufacture. L. Schwartz and J. P. Russell. —p. 1581.
*Protection Test in Mice for Identification of Leptospirosis Icterohemorrhagica (Weil's Disease). C. L. Larson.—p. 1593.
Study of Relative Toxicity of Molecular Components of Lead Arsenate. L. T. Fairhall and J. W. Miller.—p. 1610.

56:1637-1672 (Aug. 15) 1941

Observations on Use of "Phenol" Larvicides for Mosquito Control. F. L. Knowles, W. V. Parker and H. A. Johnson.—p. 1637.
Deposition and Removal of Lead in Soft Tissues (Liver, Kidneys and Spleen). L. T. Fairhall and J. W. Miller.—p. 1641.
Weil's Disease: Report of Fifty-One Cases Occurring in Puerto Rico and United States. C. L. Larson.—p. 1650.
Some Special Epidemiologic and Clinical Features of Plague in Northeastern Brazil. A. Macchiavello.—p. 1657.

Protection Test for Identification of Weil's Disease.—Larson describes a specific and easily interpreted mouse protection test for the diagnosis of Weil's disease. He determined the efficacy of the test by testing serums from 25 human beings, 13 wild rats and 1 dog suffering from leptospirosis for the presence of specific protective antibodies against Leptospira icterohemorrhagiae. Material from 3 rabbits hyperimmunized against L. icterohemorrhagiae was also tested. Protective antibodies were detected in all of the serums. No protective antibodies against Leptospirae were produced following influenza, malaria, poliomyelitis, Rocky Mountain spotted fever, typhus, Q fever, tularemia, rat-bite fever, relapsing fever, infectious jaundice, syphilis and yellow fever. Indefinite results were obtained with serums derived from rabbits hyperimmunized against Leptospira canicola. The author found that protective antibodies against Weil's disease develop during the second week of the disease and persist for at least five years. The protective antibody titer roughly follows the agglutinin titer. The test is carried out in the following manner: The kidneys and liver of a mouse dead or dying of leptospirosis are removed, weighed and finely ground in a mortar; sufficient physiologic solution of sodium chloride is added to make a 10 per cent suspension. Further tenfold dilutions are made of this suspension so that final dilutions from 1:100 to 1:100,000 are obtained. The serums to be tested are diluted to 1:100 with saline solution and passed through a Berkefeld N filter to insure sterility. Equal quantities of the diluted serum and tissue suspensions diluted to 1:1,000 are mixed and allowed to stand at room temperature for one to two hours. Ten mice are inoculated intraperitoneally with 0.3 cc. of each dilution of tissue suspension and a similar number with 0.6 cc. of each serum-tissue mixture to be tested. The mice are observed for two weeks after inoculation. Those dying before the fourth day following injection are not considered, as they die of secondary infection, trauma or other conditions not due directly to the agent. All mice surviving this period are observed daily for the development of jaundice. Protection is stated in terms of mice surviving fourteen days compared to those still alive four days after inoculation.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Experimental Pathology, London

22:111-178 (June) 1941

Effect of Certain Antiseptics on Respiration of Brain Tissues in Vitro. M. C. Manifold.—p. 111.
Antilymphocytic Serum. A. H. Cruickshank.—p. 126.
Nature of Antibacterial Agents Present in Pseudomonas Pyocyanea Cultures. R. Schoental.—p. 137.
Bacterial Inhibition by Aminosulfonic Analogues of Some Natural Aminocarboxylic Acids. H. McIlwain.—p. 148.
Transplantable Mammary Fibroadenoma of Rat Showing Sarcomatous Changes. F. R. Selbie.—p. 156.
Active Immunization Against Epidemic Typhus by Means of Vaccines Prepared from Endemic Virus. M. Ruiz Castaneda.—p. 167.
Oxygen Labile Hemolysin or Toxin of Clostridium Welchii. E. W. Todd.—p. 172.

Active Immunization Against Epidemic Typhus.—Ruiz Castaneda used typhus vaccines prepared from endemic virus for immunization against epidemic typhus. The virus used for preparing the vaccines was the L strain obtained from a typhus patient in Mexico City in 1936. It has the properties of murine virus and therefore grows readily in the guinea pig tunica vaginalis and in the peritoneum of irradiated rats. The lungs of mice inoculated with peritoneal rat washings shown to be rich in rickettsias and free of bacteria by staining are pooled and emulsified; from 5 to 7 cc. of citrate solution is used for each pair of lungs. The tissue emulsion is lightly centrifuged at low speed to remove gross particles and the supernatant material is checked microscopically for richness and purity. Lung emulsions contain an abundance of rickettsias and are suitable for passage by intranasal instillation in rats, but because of the frequency of bacterial contaminants and pneumonia in rats the author built up the potency of the inoculum by the guinea pig rat-mouse passage sequence. Previous reports indicated that small amounts of the lung vaccine protected guinea pigs against infection by the L strain of murine typhus virus. Using a vaccine having a turbidity of 2 on the McFarland scale, Finlayson and Grobler reported successful protection of guinea pigs against infection by both endemic and epidemic virus from South Africa; 1 cc. protected against the endemic strains and two such doses against epidemic strains. If the vaccine was concentrated to one-half its original volume by precipitation with alum, animals were protected against the epidemic strain by a single 1 cc. dose. Because of the practical importance of the problem the author attempted to determine the minimal quantity of murine lung vaccine necessary to protect against classic European typhus. The Breinl strain was used as a test virus. The dose required to produce certain infection in all unvaccinated controls represented 0.2 Gm. of infected guinea pig brain prepared as a lightly centrifugated emulsion. The vaccine was standardized by the nephelometric method and was administered in 1 cc. doses at weekly intervals. Fourteen animals considered protected that received an average dose of 2.78 cc. of lung vaccine equivalent to a turbidity of 2 on the McFarland scale had an average of thirty-five hundredths day of fever. However, 10 partially protected animals received an average dose of 1.25 cc. and had an average of two and nine-tenths days of fever, while 3 unprotected guinea pigs had an average dose of 1.15 cc. and seven days of fever. Even a single 1 cc. dose of a vaccine of high antigenic content given to 8 guinea pigs conferred a considerable degree of protection. However, doses of vaccines of lower rickettsia content should be multiple.

British Journal of Ophthalmology, London

25:349-396 (Aug.) 1941

Mechanism of Intraocular Pressure in Mammalia. T. Henderson.—p. 349.
Distance Object Test Type for Children. F. E. Preston.—p. 357.
Argyrosis of Conjunctiva, Cornea and Tear Sac. A. Loewenstein.—p. 360.
Retinopathia Centralis Angiospastica (Angioneurotica) and Serosa Allergica, and Their Relation to Detachment of Retina. A. Loewenstein.—p. 369.
Blue Sclerotics: Case. J. P. S. Walker.—p. 383.

British Medical Journal, London

2:187-216 (Aug. 9) 1941

The Mental Defective in the Army. F. J. S. Esher.—p. 187.
Hypoprothrombinemia and Avitaminosis K in Man. R. Kark and A. W. Souter.—p. 190.
Rupture of Drumhead as Wartime Injury. A. B. Alexander.—p. 195.
Recovery from Uremia Following Crush Injury. R. G. Henderson.—p. 197.
Allergic Shock Following Schultz-Charlton Test. R. M. Calder.—p. 198.

Glasgow Medical Journal

18:33-54 (Aug.) 1941

Unusual Case of Staphylococcic Pyemia. J. W. Hamilton and L. W. Price.—p. 33.

Journal of Physiology, Cambridge

100:1-124 (Aug.) 1941

Potassium Accumulation in Muscle and Associated Changes. P. J. Boyle and E. J. Conway.—p. 1.
Pharmacologic Actions of Morphothebaine-Dimethylether. J. A. Gunn.—p. 64.
Influence of Secretin on Pancreatic Secretion in Cat. E. J. W. Barrington.—p. 80.
Hemopoietic Activity of Mammalian Livers. F. X. Aylward, W. S. M. Grieve, B. R. S. Mainwaring and J. F. Wilkinson.—p. 94.
Influence of Anterior Pituitary Extracts on Insulin Content of Pancreas of Hypophysectomized Rat. M. Griffiths.—p. 104.
Antagonism Between Insulin and Posterior Lobe Pituitary Extract. M. Griffiths.—p. 112.
Permeability Change of Stimulated Nerve. J. F. Danielli.—p. 117.

Lancet, London

2:149-176 (Aug. 9) 1941

*Study of Pathogenesis of Thyrotoxicosis. F. F. Rundle.—p. 149.
Psychiatric Reactions of Civilians in War Time. A. Harris.—p. 152.
Calcium and Phosphorus Studies in Parathyroid Tetany. J. D. Robertson.—p. 156.
Recovery from Crush Syndrome: Case. C. J. Longland and J. Murray.—p. 158.
Isolation of Hemolytic Streptococci from Wounds. A. E. Francis.—p. 159.
Cerebral Hemorrhage in Infant Born by Cesarean Section. C. P. Lapage.—p. 160.

Pathogenesis of Thyrotoxicosis.—Rundle states that, although the ocular component and thyroid intoxication are usually associated, they may occur as independent phenomena. Thus in 332 consecutive instances of thyrotoxicosis there was retraction of the lids or proptosis or both in about 3 of every 4 patients. But ocular signs without goiter or hypermetabolism are not rare. The clinical evidence that the ocular changes have an extrathyroid origin supports the pituitary theory of exophthalmic goiter. Experimental data provide the most suggestive evidence. Extracts of anterior lobe not only activate the thyroid and cause secondarily all the manifestations of thyrotoxicity but also result in exophthalmos. Some of the clinical factors associated with the onset of thyrotoxicosis appear to act by disturbing the higher controlling mechanism of the gland. There is evidence also that the responsiveness of the thyroid epithelium is variable. Certain thyroid conditions, notably simple goiter, may predispose to the thyroid intoxication of exophthalmic goiter. Therefore it is convenient to speak of pituitary and thyroid factors in the pathogenesis of thyrotoxicosis. There was a family history of thyroid disease in 22 per cent of the 322 patients with thyrotoxicosis. Antecedent simple goiter had been present in 18 per cent, it was associated with psychic trauma with the onset of symptoms in 42 per cent and the disease developed within two years of the menopause in 20 per cent. When a psychopathic personality or a psychic trauma is associated with the onset, psychoneurosis may coexist with thyrotoxicosis, but it is not an integral part of the syndrome. Follow-up studies show a comparatively heavy incidence of nervous disorder after thyroidectomy. This seems to favor the concept of thyrotoxicosis as a general neuroendocrine disorder in which thyroidectomy removes only the most important of the glandular components, leaving untouched the fundamental disorder. It has been claimed (Crile 1935) that persistent hyperexcitability suggests that a constitutional sympatheticotonia forms the background on which thyroid hyperplasia develops. Although it is possible that a labile autonomic nervous system predisposes to thyrotoxicosis, it is doubtful whether a division of that system is especially affected.

third of the patients with the atrophic type of gastritis complained of fatigue. It was absent in the hypertrophic group. The correlated data show that except for fatigability and absence of epigastric complaint in 2 patients with atrophic gastritis the symptoms of hypertrophic and atrophic gastritis are similar. Ten of the 75 patients had symptoms characteristic of peptic ulcer. Roentgen observations were of inconsequential value as a direct aid in the diagnosis of gastritis. However, barium gastrointestinal studies were of value in determining the presence or absence of esophageal lesions, cancer, ulcer of the stomach, pyloric obstruction, duodenal ulcer and lesions elsewhere in the small or large intestine.

Aviation Medicine.—Fulton summarizes the recent literature on aviation medicine. The limitations of air combat rest more with the pilot than with the plane, and the government that succeeds in adequately protecting the pilot through study of his physiologic needs will have a decisive strategic advantage in combat. Modern combat flying, especially the dive bombing maneuver, causes the development of centrifugal forces along the longitudinal axis of the body drawing blood away from the head and causing collapse from acute cerebral anoxia. A healthy young adult can withstand a positive acceleration along the vertical axis of the body of 4.5 g (four and a half times the force of gravity) for approximately five seconds. But from the point of view of safety in aviation the pilot's coordination prior to loss of consciousness is vital. The condition of the organism determines the capacity to withstand acceleration; an alcoholic spree and an empty stomach diminish it. The German literature also states that the following favor the pilot's capacity: inhalation of 5 or 6 per cent carbon dioxide, vasoconstrictor drugs, increase in the tone of the capillary wall, posture and mechanical constriction of the abdomen and of the lower extremities by pneumatic belts and trousers. The Germans favor a crouching position, with the legs flexed against the abdomen. All factors that tend to improve the body's resistance to positive acceleration are those that keep blood in the head. Recently the use of oxygen in low altitude ranges has become an established practice to avert impairment in mental functions as it has among high altitude squadrons for the sake of washing out nitrogen. For the breathing of oxygen an ideal face mask is yet to be found. For supplying oxygen the new aluminum alloy tanks weigh much less than the old tanks but they are more vulnerable to machine gun penetration and are probably a greater hazard to the pilot and the ship than the heavy tanks. Pressure cabin planes have not proved feasible for light combat aircraft. The experiencing by high altitude pilots of symptoms similar to those of bends not attributable to anoxia, acceleration or metabolic disturbance has been thought to be due to sudden pulmonary air embolism. Direct proof that high altitude bends are caused by the liberation of nitrogen has not been established, but the similar symptoms make indirect evidence highly impressive. Tests in decompression chambers suggest that at least 50 per cent of young male adults can withstand altitudes up to 40,000 feet for from one to six hours without bends developing. Hence high altitude squadrons should be selected on the basis of these tests. The replacing of nitrogen with helium or by preoxygenation is not feasible, but with the delaying effects of pure oxygen from the ground up bends may cease to be a serious problem in military aviation. Regarding anoxia of the adrenals, it is not yet clear whether the administration of adrenal cortex extract would facilitate the pilot's adjustment to high altitudes or improve his performance.

Northwest Medicine, Seattle

40:265-308 (Aug.) 1941

Cerebral Birth Injury. M. G. Peterman, Milwaukee.—p. 267.
Glucose-Insulin Treatment in Hyperemesis Gravidarum. D. F. Bice, Yakima, Wash.—p. 270.
Practical and Inexpensive Plasma Bank. L. J. Rosellini, Mildred Porter and C. R. Jensen, Seattle.—p. 272.
Total Gastrectomy for Diffuse Superficial Carcinoma. J. W. Baker, Seattle.—p. 277.
Curare and Scopolamine in Convulsive Therapy. R. J. Bennett, Fort Steilacoom, Wash.—p. 280.
Meningococcic Septicemia: Prolonged Case Treated with Three Sulfonamide Drugs. Marian G. Hayes, Eugene, Ore.—p. 284.
Bone Tumor: Problem of Diagnosis. C. G. Bain, Chehalis, Wash.—p. 287.

Ohio State Medical Journal, Columbus

37:725-820 (Aug.) 1941

Diet, Health and Defense. C. A. Elvehjem, Madison, Wis.—p. 741.
Method for Instilling Iodized Oil in Trachea for X-Rays. J. R. Jarvis, Van Wert.—p. 746.
Previous Uterine Infection as Predisposing Cause for Spontaneous Rupture of Uterus. J. G. Fleming, Cincinnati.—p. 747.
Thrombosis and Embolism of Abdominal Aorta: Report of Case with Obstruction of Renal Arteries. M. L. Siegel and C. F. Garvin, Cleveland.—p. 750.
Chills and Fever as Manifestation of Sulfathiazole Toxicity. W. E. Molle and W. Buck, Cincinnati.—p. 752.
Acute Suppurative Nephritis Following Hysterectomy: Case Report. E. Eichner, Cleveland.—p. 754.
Clinical Aspects of Malignancy of Lung: Case Reports. O. Berghausen, Cincinnati.—p. 757.
Craniocerebral Injuries. J. N. Wychgel and W. J. Urbanski, Cleveland. —p. 761.
Thoracentesis of Chest—Inexpensive Method. A. A. Roth, Cleveland.—p. 764.
Surgical Relief of Intractable Pain in Upper Extremity Due to Malignant Disease. L. M. Weinberger, Chicago.—p. 765.
Specific Therapy in Coseasonal Management of Hay Fever: Importance of Controlled Variation of Dosage. L. E. Seyler, Dayton.—p. 768.
Unilateral Exophthalmos and Spinal Cord Compression in Case of Multpile Myeloma. J. Flynn and S. Sailer, Cincinnati.—p. 771.

Public Health Reports, Washington, D. C.

56:1581-1636 (Aug. 8) 1941

Skin Hazards in Airplane Manufacture. L. Schwartz and J. P. Russell. —p. 1581.
*Protection Test in Mice for Identification of Leptospirosis Icterohemorrhagica (Weil's Disease). C. L. Larson.—p. 1593.
Study of Relative Toxicity of Molecular Components of Lead Arsenate. L. T. Fairhall and J. W. Miller.—p. 1610.

56:1637-1672 (Aug. 15) 1941

Observations on Use of "Phenol" Larvicides for Mosquito Control. F. L. Knowles, W. V. Parker and H. A. Johnson.—p. 1637.
Deposition and Removal of Lead in Soft Tissues (Liver, Kidneys and Spleen). L. T. Fairhall and J. W. Miller.—p. 1641.
Weil's Disease: Report of Fifty-One Cases Occurring in Puerto Rico and United States. C. L. Larson.—p. 1650.
Some Special Epidemiologic and Clinical Features of Plague in Northeastern Brazil. A. Macchiavello.—p. 1657.

Protection Test for Identification of Weil's Disease.—Larson describes a specific and easily interpreted mouse protection test for the diagnosis of Weil's disease. He determined the efficacy of the test by testing serums from 25 human beings, 13 wild rats and 1 dog suffering from leptospirosis for the presence of specific protective antibodies against Leptospira icterohemorrhagiae. Material from 3 rabbits hyperimmunized against L. icterohemorrhagiae was also tested. Protective antibodies were detected in all of the serums. No protective antibodies against Leptospirae were produced following influenza, malaria, poliomyelitis, Rocky Mountain spotted fever, typhus, Q fever, tularemia, rat-bite fever, relapsing fever, infectious jaundice, syphilis and yellow fever. Indefinite results were obtained with serums derived from rabbits hyperimmunized against Leptospira canicola. The author found that protective antibodies against Weil's disease develop during the second week of the disease and persist for at least five years. The protective antibody titer roughly follows the agglutinin titer. The test is carried out in the following manner: The kidneys and liver of a mouse dead or dying of leptospirosis are removed, weighed and finely ground in a mortar; sufficient physiologic solution of sodium chloride is added to make a 10 per cent suspension. Further tenfold dilutions are made of this suspension so that final dilutions from 1:100 to 1:100,000 are obtained. The serums to be tested are diluted to 1:100 with saline solution and passed through a Berkefeld N filter to insure sterility. Equal quantities of the diluted serum and tissue suspensions diluted to 1:1,000 are mixed and allowed to stand at room temperature for one to two hours. Ten mice are inoculated intraperitoneally with 0.3 cc. of each dilution of tissue suspension and a similar number with 0.6 cc. of each serum-tissue mixture to be tested. The mice are observed for two weeks after inoculation. Those dying before the fourth day following injection are not considered, as they die of secondary infection, trauma or other conditions not due directly to the agent. All mice surviving this period are observed daily for the development of jaundice. Protection is stated in terms of mice surviving fourteen days compared to those still alive four days after inoculation.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Experimental Pathology, London

22:111-178 (June) 1941

Effect of Certain Antiseptics on Respiration of Brain Tissues in Vitro. M. C. Manifold.—p. 111.
Antilymphocytic Serum. A. H. Cruickshank.—p. 126.
Nature of Antibacterial Agents Present in Pseudomonas Pyocyanea Cultures. R. Schoental.—p. 137.
Bacterial Inhibition by Aminosulfonic Analogues of Some Natural Aminocarboxylic Acids. I. L. McIlwain.—p. 148.
Transplantable Mammary Fibroadenoma of Rat Showing Sarcomatous Changes. F. R. Selbie.—p. 156.
*Active Immunization Against Epidemic Typhus by Means of Vaccines Prepared from Endemic Virus. M. Ruiz Castaneda.—p. 167.
Oxygen Labile Hemolysin or Toxin of Clostridium Welchii. E. W. Todd.—p. 172.

Active Immunization Against Epidemic Typhus.—Ruiz Castaneda used typhus vaccines prepared from endemic virus for immunization against epidemic typhus. The virus used for preparing the vaccines was the L strain obtained from a typhus patient in Mexico City in 1936. It has the properties of murine virus and therefore grows readily in the guinea pig tunica vaginalis and in the peritoneum of irradiated rats. The lungs of mice inoculated with peritoneal rat washings shown to be rich in rickettsias and free of bacteria by staining are pooled and emulsified; from 5 to 7 cc. of citrate solution is used for each pair of lungs. The tissue emulsion is lightly centrifuged at low speed to remove gross particles and the supernatant material is checked microscopically for richness and purity. Lung emulsions contain an abundance of rickettsias and are suitable for passage by intranasal instillation in rats, but because of the frequency of bacterial contaminants and pneumonia in rats the author built up the potency of the inoculum by the guinea pig rat-mouse passage sequence. Previous reports indicated that small amounts of the lung vaccine protected guinea pigs against infection by the L strain of murine typhus virus. Using a vaccine having a turbidity of 2 on the McFarland scale, Finlayson and Grobler reported successful protection of guinea pigs against infection by both endemic and epidemic virus from South Africa; 1 cc. protected against the endemic strains and two such doses against epidemic strains. If the vaccine was concentrated to one-half its original volume by precipitation with alum, animals were protected against the epidemic strain by a single 1 cc. dose. Because of the practical importance of the problem the author attempted to determine the minimal quantity of murine lung vaccine necessary to protect against classic European typhus. The Breinl strain was used as a test virus. The dose required to produce certain infection in all unvaccinated controls represented 0.2 Gm. of infected guinea pig brain prepared as a lightly centrifugated emulsion. The vaccine was standardized by the nephelometric method and was administered in 1 cc. doses at weekly intervals. Fourteen animals considered protected that received an average dose of 2.78 cc. of lung vaccine equivalent to a turbidity of 2 on the McFarland scale had an average of thirty-five hundredths day of fever. However, 10 partially protected animals received an average dose of 1.25 cc. and had an average of two and nine-tenths days of fever, while 3 unprotected guinea pigs had an average dose of 1.15 cc. and seven days of fever. Even a single 1 cc. dose of a vaccine of high antigenic content given to 8 guinea pigs conferred a considerable degree of protection. However, doses of vaccines of lower rickettsia content should be multiple.

British Journal of Ophthalmology, London

25:349-396 (Aug.) 1941

Mechanism of Intraocular Pressure in Mammalia. T. Henderson.—p. 349.
Distance Object Test Type for Children. F. E. Preston.—p. 357.
Argyrosis of Conjunctiva, Cornea and Tear Sac. A. Loewenstein.—p. 360.
Retinopathia Centralis Angiospastica (Angioneurotica) and Serosa Allergica, and Their Relation to Detachment of Retina. A. Loewenstein.—p. 369.
Blue Sclerotics: Case. J. P. S. Walker.—p. 383.

British Medical Journal, London

2:187-216 (Aug. 9) 1941

The Mental Defective in the Army. F. J. S. Esher.—p. 187.
Hypoprothrombinemia and Avitaminosis K in Man. R. Kark and A. W. Souter.—p. 190.
Rupture of Drumhead as Wartime Injury. A. B. Alexander.—p. 195.
Recovery from Uremia Following Crush Injury. R. G. Henderson.—p. 197.
Allergic Shock Following Schultz-Charlton Test. R. M. Calder.—p. 198.

Glasgow Medical Journal

18:33-54 (Aug.) 1941

Unusual Case of Staphylococcic Pyemia. J. W. Hamilton and L. W. Price.—p. 33.

Journal of Physiology, Cambridge

100:1-124 (Aug.) 1941

Potassium Accumulation in Muscle and Associated Changes. P. J. Boyle and E. J. Conway.—p. 1.
Pharmacologic Actions of Morphothebaine-Dimethylether. J. A. Gunn.—p. 64.
Influence of Secretin on Pancreatic Secretion in Cat. E. J. W. Barrington.—p. 80.
Hemopoietic Activity of Mammalian Livers. F. X. Aylward, W. S. M. Grieve, B. R. S. Mainwaring and J. F. Wilkinson.—p. 94.
Influence of Anterior Pituitary Extracts on Insulin Content of Pancreas of Hypophysectomized Rat. M. Griffiths.—p. 104.
Antagonism Between Insulin and Posterior Lobe Pituitary Extract. M. Griffiths.—p. 112.
Permeability Change of Stimulated Nerve. J. F. Danielli.—p. 117.

Lancet, London

2:149-176 (Aug. 9) 1941

*Study of Pathogenesis of Thyrotoxicosis. F. F. Rundle.—p. 149.
Psychiatric Reactions of Civilians in War Time. A. Harris.—p. 152.
Calcium and Phosphorus Studies in Parathyroid Tetany. J. D. Robertson.—p. 156.
Recovery from Crush Syndrome: Case. C. J. Longland and J. Murray.—p. 158.
Isolation of Hemolytic Streptococci from Wounds. A. E. Francis.—p. 159.
Cerebral Hemorrhage in Infant Born by Cesarean Section. C. P. Lapage.—p. 160.

Pathogenesis of Thyrotoxicosis.—Rundle states that, although the ocular component and thyroid intoxication are usually associated, they may occur as independent phenomena. Thus in 332 consecutive instances of thyrotoxicosis there was retraction of the lids or proptosis or both in about 3 of every 4 patients. But ocular signs without goiter or hypermetabolism are not rare. The clinical evidence that the ocular changes have an extrathyroid origin supports the pituitary theory of exophthalmic goiter. Experimental data provide the most suggestive evidence. Extracts of anterior lobe not only activate the thyroid and cause secondarily all the manifestations of thyrotoxicity but also result in exophthalmos. Some of the clinical factors associated with the onset of thyrotoxicosis appear to act by disturbing the higher controlling mechanism of the gland. There is evidence also that the responsiveness of the thyroid epithelium is variable. Certain thyroid conditions, notably simple goiter, may predispose to the thyroid intoxication of exophthalmic goiter. Therefore it is convenient to speak of pituitary and thyroid factors in the pathogenesis of thyrotoxicosis. There was a family history of thyroid disease in 22 per cent of the 322 patients with thyrotoxicosis. Antecedent simple goiter had been present in 18 per cent, it was associated with psychic trauma with the onset of symptoms in 42 per cent and the disease developed within two years of the menopause in 20 per cent. When a psychopathic personality or a psychic trauma is associated with the onset, psychoneurosis may coexist with thyrotoxicosis, but it is not an integral part of the syndrome. Follow-up studies show a comparatively heavy incidence of nervous disorder after thyroidectomy. This seems to favor the concept of thyrotoxicosis as a general neuroendocrine disorder in which thyroidectomy removes only the most important of the glandular components, leaving untouched the fundamental disorder. It has been claimed (Crile 1935) that persistent hyperexcitability suggests that a constitutional sympatheticotonia forms the background on which thyroid hyperplasia develops. Although it is possible that a labile autonomic nervous system predisposes to thyrotoxicosis, it is doubtful whether a division of that system is especially affected.

Schweizerische medizinische Wochenschrift, Basel

71:701-732 (June 7) 1941

Estimation and Treatment of Neurotics in Active Military Service. R. Brun.—p. 701.
Psychohygiene in Front Line. M. Boss.—p. 707.
Therapeutic Problems in Work of Psychiatric Consultation Office in Military Medical Institute. K. Binswanger.—p. 711.
*Vitamin C and Military Sport. H. Brunner.—p. 715.
Directing Lines for Localization and Removal of Foreign Bodies in War Injuries. A. Zuppinger.—p. 716.
Wire Screen Chin Cap: Suggestion for First Aid for Jaw Injuries in the Field. W. Roos.—p. 719.
Bilateral Avulsion of Spina Iliaca Anterior Inferior. W. Bachmann.—p. 721.
Psychology of Obstinacy in Military Service. T. Bovet.—p. 722.

Vitamin C and Military Sport.—Brunner calls attention to the fact that the marching contest of the Swiss army, with full pack, over a distance of 41 kilometers, with a grade of 500 meters, makes great demands on the physical endurance of men. He studied the physical condition of 10 men who were subjected to an intensive preparatory training. To obtain optimal physical performance capacity, 300 mg. of a vitamin C preparation was given daily until the vitamin was excreted in the urine. When this took place the daily dose was reduced to 200 mg. The saturation experiment disclosed vitamin C deficiencies of from 600 to 1,800 mg., on the average of 1,210 mg. It is noteworthy that two men who were abstinents had the lowest vitamin deficiency. During the period of training the daily vitamin C requirement was 200 mg. Muscular pains brought on by the intense training subsided under the influence of vitamin C medication. Eight of the 10 men were able to take part in the marching contest. Their performance was satisfactory. All completed the contest. Whereas many of those who did not receive vitamin C developed muscular spasms in the course of the march, only one of the author's men manifested this symptom and for only a brief period. After a short rest period (two hours) the physical and mental fatigue was slight. All the men who were given vitamin C expressed satisfaction with the effect. They felt fresher, stronger and better able to stand the exertion. Especially gratifying was the efficacy of the vitamin against muscular pains.

Bollettino, Milan

11:205-234 (Oct.-Nov.-Dec.) 1939. **Partial Index**

Treatment of Whooping Cough in Blood Serum of Convalescents from Parotitis. S. Saggese.—p. 212.

Parotitic Blood Serum in Whooping Cough.—Saggese observed an epidemiologic antagonism between parotitis and whooping cough. The latter was permanently arrested in several patients when parotitis had developed. He had also observed that children suffering from parotitis either do not develop whooping cough or have it in attenuated form. Saggese injected blood serum obtained from convalescents in the second or third week of parotitis in 23 patients with whooping cough. Improvement was evident after the first or second intramuscular injection of 8 cc. of serum, and a cure was obtained after the third.

Arch. Clín. e Inst. endocrinol., Montevideo

1:605-932 (No. 2) 1937-1940. **Partial Index**

*Action of Vitamin B_1 in Funicular Myelosis of Pernicious Anemia. J. C. Mussio Fournier and F. Rawak.—p. 637.

Vitamin B_1 in Funicular Myelosis.—Mussio Fournier and Rawak report the case of an apparently normal woman, aged 54, who complained of glossitis. Three years later the patient exhibited pernicious anemia and symptoms of acute funicular myelosis of the pseudotabes type. Paralysis began in the legs and rapidly involved the trunk and the arms. Raw liver by mouth and injections of liver extract and of vitamin B_1 were administered. Vitamin B_1 was given in daily doses of 10 mg. for the first twenty-four days and of 2 mg. for the following days up to a total of 300 mg. in three months. The neurologic symptoms improved early in the course of the treatment, even before the change in the blood picture. The more recent symptoms showed earlier and more complete improvement. By the end of the treatment the muscles of the trunk, arms and hands were normal; those of the legs were almost normal. The patient was able to walk alone. The glossitis has disappeared. The author believes that vitamin B_1 is a specific in the therapy of the neurologic symptoms of pernicious anemia and that the earlier the treatment the better the results.

Medizinische Klinik, Berlin

37:501-524 (May 16) 1941. **Partial Index**

Clinical Observations on Serious Familial Botulism Infection. G. Breitzke.—p. 507.
*Practical Experiences with Simultaneous Vaccination and Active Immunization with Diphtheria Toxoid in an Epidemic of Diphtheria. Zippel. —p. 510.
Cause and Estimation of Heterotopic Stimulus Formation on Heart. F. Brauch.—p. 511.

Active Immunization in Diphtheria.—Zippel reports that when an epidemic of diphtheria developed in a large orphan home active immunization was at once instituted. Approximately 500 children were given a single administration of toxoid. At the same time they were given 2,000 units of diphtheria serum. This procedure greatly reduced the number of new cases, and those which developed were atypical. To prevent further development of cases, the children were given a second dose of toxoid six months after the first. Two vaccinations protected a large percentage of children against diphtheria. If vaccinated children develop an angina with diphtheria-like odor (particularly during the first few months after vaccination) the possibility of an atypical diphtheria should be considered and serum treatment instituted. From his experiences with smears, the author concludes that they are of little value in the diagnosis of diphtheria. Children should be vaccinated against diphtheria before they enter school. The vaccinations should be done during the season that is free from epidemics of diphtheria. Active immunization against diphtheria is especially important in institutes and homes for children; not only should all inmates be vaccinated against diphtheria, but the newly admitted should be currently immunized.

Maandschrift voor Kindergeneeskunde, Leyden

10:219-266 (March) 1941. **Partial Index**

*Nasal Allergy in Children. H. A. E. van Dishoeck.—p. 232.
*Acute Pancreatitis in Connection with Mumps: Case. J. M. C. Visscher-Jolles.—p. 259.

Nasal Allergy in Children.—Among 500 children varying in age between 3 and 15 years with otorhinolaryngologic disorders, van Dishoeck discovered 65 in whom allergy was suspected. Fifty (10 per cent) of the total number showed positive cutaneous reactions, chiefly for inhalants but in some cases also for food allergens. Sensitization to more than one allergen was present in 41 cases; only 3 uncomplicated cases of hay fever were found. In 35 cases asthmatic complaints were present. Cutaneous reactions were positive most frequently with house dust, pollen and feathers. Eggs and milk produced positive reaction in 3 and 2 cases, respectively. The number of eosinophils and lymphocytes in the blood were nearly always considerably increased. Eosinophils in the nasal mucus, allergic edema of the antrums, allergic degeneration of the turbinates, eczema during infancy and a family history of allergy were demonstrable in about half of the cases. Many patients were cured by elimination of the offensive allergens. Patients with hypersensitivity to house dust were successfully desensitized. The author thinks that the detection and treatment of nasal allergy in children will be of great importance for the prevention of asthma in adults.

Concurrence of Acute Pancreatitis with Mumps.—Visscher-Jolles reports the clinical history of a boy aged 8 months. When the author first saw him, two days after the first signs of indisposition, the child was in a deep coma. Examination disclosed hyperglycemia and severe leukocytosis, and the diastase ferment content of the urine was extremely low. The disorder was diagnosed as acute pancreatitis. The child recovered. Although acute pancreatitis is usually rapidly fatal, the form that complicates infectious diseases is rarely fatal. It is possible that in the case under consideration the pancreatitis was brought on by mumps. An epidemic of mumps existed at the time in the school attended by the siblings of the boy, and a brother had been at home with mumps the week preceding the development of the disease.

Book Notices

Fit to Fly: A Medical Handbook for Fliers. By Malcolm C. Grow, M.D., Lt. Col., Medical Corps, United States Army, and Harry G. Armstrong, B.S., M.D., Captain, Medical Corps, United States Army. Cloth. Price, $2.50. Pp. 387, with 29 illustrations. New York & London: D. Appleton-Century Company, Incorporated, 1941.

Colonel Grow and Captain Armstrong have produced a well written, easily understandable and timely volume to acquaint and equip both nonfliers and fliers with information concerning the reactions of the human body to the rapidly changing environmental effects encountered while in the air. The book begins with the subject of medicine in aviation; it then passes on to the protective health measures of the aviator (hygiene) and proceeds to the physical examination of the flier. Thereafter the writers discuss the body reactions to altitude, oxygen deprivation, atmospheric pressure changes, acceleration and deceleration, sensory illusions, and fatigue in flight. A chapter is devoted to aviation accidents and first aid. Protective devices to prevent untoward effects of flying are discussed. Because of the wide ranges of fliers into distant lands and different climates, the final chapter of the book is devoted to tropical diseases and ailments most likely to be encountered. The book should be of pronounced value to those who take to the air and should be of direct benefit to aviators so that they can "keep them flying."

The Development of the Sciences: A Series of Lectures Delivered at Yale University Under the Auspices of the Yale Chapter of Gamma Alpha. Second Series. By Oystein Ore, Frank Schlesinger, Henry Margenau, John Arrend Timm, Chester Ray Longwell, Lorande Loss Woodruff, Walter Richard Miles and John Farquhar Fulton. Edited by L. L. Woodruff. Cloth. Price, $3. Pp. 336, with one illustration. New Haven: Yale University Press; London: Oxford University Press, 1941.

Occasionally there appears a collection of lectures that offers interesting and thought provoking reading for every one regardless of his field of specialization: The Development of the Sciences is one of these collections. The material in this book represents the fields of mathematics, astronomy, chemistry, physics, geology, biology, psychology and medicine and was first offered during the winter and spring of 1940 as a series of lectures sponsored by the Yale University chapter of Gamma Alpha. As these lectures were designed for the general public, the authors have made no attempt to become technical; yet the sciences are traced from their beginnings to the more modern trends with no loss of interest. The articles are so forcefully written and the material so absorbing that the reader will loathe interruptions.

Every chapter is so well written that all must be commended. However, the discussions on astronomy, biology, psychology and medicine will be of particular interest to the physician. Astronomy has always intrigued man, partly because of the mysticism associated with this science. The description of the earlier studies by the Greeks cogently visualizes the slow and tedious deductions often necessary as the prelude to subsequent exciting findings. The names of Galileo and Bacon are familiar to every one, but this chapter acquaints the reader with the less well known but equally important contributors of earlier and later eras. The close relationship between mathematics, physics and astronomy and the part it has played in the development of our other sciences offers a fitting background for the promotion of a more avid interest in subjects which may be neglected in our time pressed days. Who can fail to appreciate the romantic possibilities of Franklin's famous kite experiment and Galvani's accidental discovery of the convulsive movements of the frog's leg while preparing a broth from these legs for his wife, who was suffering from a chest ailment?

Huxley has said that medicine is the foster mother of chemistry, botany and comparative anatomy and physiology. The farewell chapter was to have been written by Dr. Harvey Cushing, but after his untimely death Dr. John F. Fulton agreed to undertake the assignment. He has attained the same degree of sustained literary entertainment that the other chapters hold. This volume will be well received by those who are in the habit of keeping a book by their bedside or favorite easy chair.

Der Rücken des Menschen, die Erkennung und Behandlung seiner Erkrankungen: Eine Anleitung für Studierende der Medizin und praktische Aerzte. Von Prof. Dr. med. O. Veraguth, und Dr. med C. Braendli-Wyss. Cloth. Price, 20 Swiss francs; 12 marks. Pp. 232, with 96 illustrations. Bern: Hans Huber, 1940.

The author illustrates by diagrams of trunk and body posture and an elaborate system of lines and landmarks the technic of determining asymmetry. He describes in detail inspection of the back, palpation of the back and passive movements of the neck and head. He has copied Mennell's interesting and instructive series of diagrams of back examination and manipulation. His description of cutaneous sensation is excellent. He describes the interesting sinuvertebral nerve, which did not figure prominently in the English literature until emphasized by Steindler. He makes an interesting division of the lumbalgias into those due to traumatic muscular involvement, rheumatic muscular involvement, tendoperiosteal, neuritic, muscular, ligamentous, articular, ex-articular and osseous. It appears to be a highly technical description for medical students and general practitioners.

Introduction to Physical Biochemistry. By J. M. Johlin, Ph.D., D.Sc., Associate Professor of Biochemistry in the Vanderbilt University School of Medicine, Nashville. Cloth. Price, $2.75. Pp. 231, with 10 illustrations. New York & London: Paul B. Hoeber, Inc., 1941.

The contents of the twelve chapters that make up this volume would have been better covered if "of the Blood" had been added to its title, for all but one of them are limited to a consideration of "the external environment of tissue cells." In toto, the book covers the application of standard physicochemical methods of analysis to the blood with the sixth chapter, however, thrown in on "characteristics of colloidal state of matter." Some historical asides here try to do justice to Thomas Graham's great discoveries and make fine reading; for the rest, however, the author believes that Graham's modern followers have added nothing that the physical chemists did not first bring in. The net result is that the blood remains an aqueous pabulum, still essentially a dilute solution, in spite of the author's warning that "a fluid such as blood cannot be considered as a simple solution"—in which ions, acids and alkalis, oxygen and carbon dioxide, colloids and crystalloids try ceaselessly to get into equilibrium. The hydronium concept replaces that of the hydrogen ion; and, to explain buffering, the proteins receive their deserved larger consideration over the once solely dominant polybasic salts. The volume (well made and available at a decent price) therefore recommends itself to all in search of the factually established and the theoretically believed. The author's scheme of presentation is excellent.

Biology of the Laboratory Mouse. By The Staff of The Roscoe B. Jackson Memorial Laboratory. Clarence C. Little, Director. George D. Snell, Editor. With a chapter on Infectious Diseases of Mice. By J. H. Dingle, Harvard Medical School, Boston. Cloth. Price, $7. Pp. 497, with 172 illustrations. Philadelphia: Blakiston Company, 1941.

This book represents an attempt to assemble widely scattered information relating to the mouse on reproduction and embryology, genetics, histology, neoplasms, endocrinology, parasitology and bacteriology. Accordingly the thirteen chapters discuss the early embryology of the mouse, reproduction, histology, spontaneous neoplasms in the mouse, gene and chromosome mutations, the genetics of spontaneous tumor formation, the genetics of tumor transplantation, endocrine secretion, the milk influence in tumor formation, inbred and hybrid animals and their value in research, parasites, infectious diseases in mice, care and recording. Several authors have combined their efforts to produce the book, each being responsible for one or more chapters. These authors, who are from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, with the exception of J. H. Dingle from Harvard Medical School, are C. C. Little, G. D. Snell, J. J. Bittner, A. M. Cloudman, E. Fekete, W. E. Heston, W. L. Russell and G. W. Woolley. The book is conducive to easy reading, the index adequate, the illustrations numerous and excellent. At the end of each chapter is a fairly extensive bibliography, a desirable feature for this type of book. The volume should be a useful addition to the laboratory library. It will serve as a ready reference for a better understanding of the biology of this useful experimental animal.

General Chemistry. By Harry N. Holmes, Professor of Chemistry in Oberlin College, Oberlin, Ohio. Fourth edition. Cloth. Price, $3.75. Pp. 720, with 199 illustrations. New York: Macmillan Company, 1941.

The present volume reflects the remarkable advances that have been made not only in chemistry but in the technic of teaching as well. Chemical textbooks of fifteen or twenty years ago seemed superb at that time and created an impression of finality —as if there were little more which could be added to the fundamentals of that science. But in this excellent volume we find discussions of many new topics, among them the structure of the atom, electrovalence, covalence, coordinate valence, the relative sizes of ions in crystals, radiation chemistry, uranium fusion, cyclotrons, vitamins, chemotherapy and strategic raw materials. Even the definitions of fundamental laws and principles have changed, and it is now noted that some of these which were once absolute and solid as the rock of Gibraltar have lost, like that rock, some of their unqualified self assurance. The subject matter is presented in a manner that holds the interest of the reader. Professor Holmes's literary style is something to be particularly noted. It has the simplicity, directness and change of pace that marks good writing. The presentation of a concept is almost invariably accompanied by a practical application or illustration that drives home the point. The text is generously supplemented with diagrams, sketches, tables and photographs. The reader is made to feel that the study of chemistry is the study of the basis of our very life and existence and not merely a discipline to hurdle on the way through college. It is altogether evident that an interesting presentation of the subject such as this can hardly fail to attract students to chemistry as a life work. This is, in the long run, perhaps the most important contribution a general textbook can make. The publishers are to be commended for the attractive manner in which the volume is designed and printed.

Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern. Die Wirbelsäulenverletzungen und ihre Ausheilung: Experimentelle, pathologisch-anatomische und röntgenologisch-klinische Untersuchungen. Von Dozent Dr. med. habil. Alfons Lob, Marine-Stabsarzt d. R. Mit einem Geleitwort von Professor Dr. G. Magnus. Fortschritte auf dem Gebiete der Röntgenstrahlen, Ergänzungsband LXI. Herausgeber: Prof. Grashey. Cloth. Price, 28.50 marks. Pp. 182, with 289 illustrations. Leipzig: Georg Thieme, 1941.

This is a comprehensive publication on the varied spinal deformities resulting from trauma. It is profusely but pertinently illustrated with both roentgen ray findings and actual pathologic specimens, illustrating both the end results in loss of bone, hypertrophies of isolated parts from fibrous and bony growth and the resultant deformities with or without compression of the spinal cord. The healing of bone with the component elements of bone, cartilage and fibrous tissue has been well presented. The roentgenographic views varying with the individual lesions of pedicles, laminas and the bodies of the vertebrae display the best standards of roentgen ray technic. Lob very properly predicates operative interventions such as spinal grafts or laminectomies. One is surprised to find only casual mention of the traumatic protrusions of vertebral disks, which now form such a fertile field for surgeons in this country.

The Principles and Practice of Ophthalmic Surgery. By Edmund B. Spaeth, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia. Second edition. Cloth. Price, $10. Pp. 886, with 1,155 illustrations. Philadelphia: Lea & Febiger, 1941.

The first edition of this valuable and popular textbook of ophthalmic surgery was reviewed in these pages on Aug. 29, 1939, a few months after the book appeared. Now comes the second edition, enlarged by some fifty pages and some hundred and twenty new illustrations. A small amount of the text has been rewritten and additions have been made to some of the chapters, notably the chapter on surgery of the extraocular muscles. In the first edition many of the illustrations, particularly the close-up photographs of the eyes, left much to be desired; these have been in part replaced. The line drawings are universally good and the color plates excellent. The printing and bookmaking are of the same high standard as in the first edition. This is one of the best of modern textbooks on ophthalmic surgery. It contains much of value for the experienced surgeon and is virtually indispensable for the beginner.

A Manual of Allergy for General Practitioners. By Milton B. Cohen, M.D., Director of The Asthma, Hay Fever and Allergy Foundation, Cleveland. Cloth. Price, $2. Pp. 156. New York & London: Paul B. Hoeber, Inc., 1941.

This little volume is essentially a brief thesis on the principles of allergy. The fourteen chapters cover most of the titles discussed in more extensive works on the subject, but in a much more sketchy manner. The author, a well known pioneer in the field and an indefatigable worker for advancements in allergy, does not propose this little book as a textbook which would give the practitioner workable information. He admits that the context is extremely elementary. The volume constitutes a clear, concise and simple statement of the fundamental knowledge necessary for the understanding of the nature of allergy, but for a working knowledge of the subject one would have to proceed to obtain information from additional sources. The status of this book can best be summarized in the words of the author when he says "When one has mastered the material in this manual, he should be ready to read the more advanced and complete discussions contained in the lists of textbooks and monographs which will be found in the bibliography."

Elimination Diets and the Patient's Allergies: A Handbook of Allergy. By Albert H. Rowe, M.D., Consultant in Allergic Diseases, Alameda County Hospital, Oakland, California. Cloth. Price, $3. Pp. 264. Philadelphia: Lea & Febiger, 1941.

In the first fifty-three pages the author covers most of the field of allergy, leaving the rest of the book to cover an excellent, but brief, discussion of various common and uncommon foods and elimination diets. The technic of management by elimination diets is discussed with the thoroughness that would be appreciated primarily by the specialist. Sample diets and recipes are given in detail. The final fifty pages are entitled "Appendix" and consist of unorganized notes on many subjects, such as vitamins, weight maintenance, environmental control, history forms and directions for pollen therapy. Briefly, the value of the book is in its discussion of foods and the author's methods of diagnosis and treatment by elimination diets. Its weakness is in the attempt to cover the entire field of allergy in addition, without trying to correlate allergy with immunology or with the general field of internal medicine.

Experimental Studies on the Effect of Sulfapyridine on Pneumococci and Gonococci. By Kai Schmith. Translated from Danish by Hans Andersen, M.D. Denne Afhandling er af det lægevidenskabelige Fakultet antaget til offentlig at forsvares for den medicinske Doktorgrad, København, 1941. Paper. Pp. 216. Copenhagen: NYT Nordisk Forlag, Arnold Busck, 1941.

This book, which is written in English with a summary in Danish, consists of an introduction, a historical survey of sulfapyridine and five chapters dealing with the action of sulfapyridine on pneumococci in vitro, the effect of sulfapyridine on experimental pneumococcic infections, studies on the resistance of pneumococci to sulfapyridine, combined sulfapyridine treatment and active or passive immunization, and the effect of sulfapyridine on gonococci. Each chapter consists of two parts, the first being a brief review of previous investigations, the second the author's investigations. In view of the general knowledge of the sulfonamides, this book would probably be of interest only to experimental workers.

The American Illustrated Medical Dictionary: A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition. By W. A. Newman Dorland, A.M., M.D., F.A.C.S., Lieut-Colonel, M.R.C., U. S. Army. With the collaboration of E. C. L. Miller, M.D. Nineteenth edition. Fabrikoid. Price, $7; Thumb-Indexed $7.50. Pp. 1,647, with 914 illustrations. Philadelphia & London: W. B. Saunders Company, 1941.

Again comes a revision of this standard medical dictionary. More than two thousand new words have been added, hundreds defined for the first time in the present edition of this book. In this revision the editorial department of the American Medical Association has cooperated. The American Illustrated Medical Dictionary is the standard adopted by the press of the American Medical Association.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

INABILITY TO GAIN WEIGHT IN APPARENTLY NORMAL MAN

To the Editor:—**A patient complains of inability to gain weight. He has never been sick except for measles, though he is now 32. He is definitely nervous but otherwise has no complaints. He eats a well rounded diet, averages 2,000 to 2,500 calories a day, and does not eat between meals. He never has headaches, has no gastrointestinal, genitourinary or cardiorenal complaints, sleeps fairly well and smokes ten cigarets a day. He exercises moderately and works in a printer's shop. Though married six years, his wife has never been pregnant. He is thin, alert, cooperative and slightly nervous. He drums with his fingers and taps with his feet unconsciously. The pupils appear slightly dilated; the eyes otherwise are normal. The thyroid is not palpable; the pulse rate is 90 at rest; the palms are sweaty. There is a slight tremor when the hands are outstretched with the fingers spread. The blood pressure is 120 systolic and 80 diastolic. Examinations are otherwise negative (including the genitals). The basal metabolic rate, repeated several times at weekly intervals, has been —28, —32, —28, —30. The machine and technic have been carefully checked and other tests have been as expected. Would hyperinsulinism explain this picture, especially the low basal metabolic rate? What other diagnosis should be considered?**

M.D., Massachusetts.

ANSWER.—There is nothing in the history as here recorded to suggest hyperinsulinism. Patients who have hyperinsulinism have a clearcut clinical syndrome associated with hypoglycemia. Symptoms appear between meals or after violent exercise and are promptly relieved by the administration of sugar or food. The diagnosis is usually not difficult and can be established by determining the level of the sugar in the blood after the patient has fasted for twenty-four hours.

As nearly as can be determined by reading this history, it seems that the patient is unduly concerned about his weight; but no record is given of his height or weight. It seems unnecessary for any patient who has never been ill to be concerned about himself. There is often no correlation between a person's weight and his health, and, as a group, underweight persons enjoy better health than those who are overweight. In all probability his size has been predetermined by his heredity and is almost certainly of no importance. Insufficient evidence is given to indicate whether the low basal metabolic rates are of any importance. Hundreds of thousands of persons who have low basal metabolic rates without myxedema are perfectly normal and feel no better when their basal metabolic rates are raised to normal. If an effort is made to raise his basal metabolic rate to between —10 per cent and 0, the patient should understand that it may make no difference whatever in the way he feels.

In conclusion, what this patient seems to need most is reassurance.

Sterility is mentioned, but no record is given as to his sperm count. If this is normal, it is probably his wife who is sterile.

TOXICITY OF VITAMINS

To the Editor:—**This office is desirous of obtaining any available information concerning possible harmful effects occasioned by overdoses of vitamins. Your courtesy in this matter is appreciated.**

Cecil G. Dunn, Captain, Q. M. C., assistant to the Quartermaster General, Washington, D. C.

ANSWER.—None of the vitamins important in human nutrition is considered toxic under ordinary circumstances. Large doses of carotene may lead to carotenemia, but reduction of the dose to an amount equivalent to 5,000 to 10,000 U. S. P. units of vitamin A daily usually leads to a reduction to normal limits of the carotene content of the blood serum. Vitamin A could be administered instead of carotene without any untoward effect. Vitamin B_1 has been thought to possess some untoward effects when administered in amounts of 10 to 20 mg. or more daily. C. A. Mills (Thiamine Overdosage and Toxicity, THE JOURNAL, May 3, 1941, p. 2101) observed symptoms similar to those obtained in cases of hyperthyroidism, but other investigators who have administered large doses of thiamine hydrochloride to patients have not observed these effects.

Large doses of vitamin C have been reported to have a slight sedative effect, but this is not well established. There is some evidence that moderately large doses of vitamin D are not as beneficial to infants as doses which more nearly meet the requirements for this vitamin, which are about 400 U. S. P. units daily. However, a definitely toxic effect has not been noted with vitamin D except when the substance is given in large doses, such as 50,000 or 100,000 U. S. P. units daily. Administration of large amounts of vitamin D in the form of irradiated ergosterol is known to be beneficial in the treatment of hypoparathyroidism because the blood serum calcium level is raised toward normal. Toxic effects have not been reported for moderate doses of vitamin E or of riboflavin. Many persons who are given 50 mg. or more of nicotinic acid will show peripheral vasodilatation with flushing and sweating, but these effects are not observed if nicotinic acid amide is used. Nicotinic acid occurs in liver largely as the amide of nicotinic acid rather than as the free acid itself.

From the foregoing data there is real reason to administer the vitamins in amounts of the same order of magnitude as the daily dietary requirements.

Overirradiation of ergosterol results in the formation of a toxic substance called toxisterol. The present day manufacture of irradiated ergosterol is generally sufficiently well controlled to guard against this possibility.

OBSCURE URTICARIA AND ANGIONEUROTIC EDEMA

To the Editor:—**A married woman aged 34 had generalized urticaria, which after twenty-four hours involved about half the body surface. There was epigastric distress followed by a convulsive seizure. There were tonic contractions of the calf and forearm muscles typical of a carpopedal spasm, accompanied by working of the face muscles and some difficulty of speech. Massage of the extremities, which felt numb, and the administration of oxygen caused some relaxation. She was given 1 cc. of epinephrine hydrochloride followed by 10 cc. of calcium gluconate intravenously. The acute symptoms were promptly relieved and the urticaria disappeared fairly rapidly. The pulse rate was 116 and the blood pressure 136 systolic and 90 diastolic during the attack. Five hours later she felt fairly well. The pulse rate was 104 and the blood pressure 124 systolic and 76 diastolic, but some further urticaria was developing. Fourteen hours after the first attack the urticaria had increased and the epigastric distress had reappeared. An intramuscular injection of 1 cc. of 1:1,000 epinephrine hydrochloride was given and was promptly followed by another convulsive seizure similar to but of shorter duration than the first. Oxygen appeared to give some relief. Both attacks were accompanied by considerable increase in urinary excretion. Several short attacks occurred on the way to the hospital. The patient was given a series of infusions and calcium gluconate and was discharged after five days with the condition undiagnosed. There were no convulsions or urticaria during this period. Blood counts and urinalysis were normal. In the two day period before the onset of symptoms the only items of diet other than what was usual were some fresh peaches and two capsules of a proprietary vaccine for colds and other infections. The past history is essentially negative. Physical examination between the attacks was negative. Could this have been an acute allergic reaction, perhaps to something in the diet, with a cerebral angioneurotic edema causing the muscular spasms and possibly by irritation of the pituitary causing the polyuria? What further investigations can be suggested?**

John F. Dixon Jr., M.D., Garden City, N. Y.

ANSWER.—The case described is one of acute urticaria or angioneurotic edema. The epigastric distress is a common feature of such attack, since the edematous lesions frequently involve the gastrointestinal tract. Furthermore, areas of localized edema may occur in other portions of the blood, producing variable combinations of symptoms, such as cerebral and laryngeal, depending on the organs involved. Increased urinary excretion is a demonstrable feature during some stage of the allergic attack such as asthma and urticaria. The concept of pituitary involvement need not be seriously considered as an explanation of the polyuria. The only unusual feature of the attacks described is the tetany. Cerebral symptoms such as unconsciousness, epileptiform convulsions and even tetany have been described as part of acute and violent allergic reactions, usually consequent on the injection of allergens, the ingestion of allergenic foods or as a part of serum sickness. A number of possible explanations can be advanced for the phenomenon of tetany depicted in this case. A parathyroid deficiency or a hypocalcemia may be considered. Angioneurotic edema of the brain or cerebral anemia due to angiospasm is a possible factor. Anoxemia also suggests itself because of the beneficial effect of oxygen inhalations. In the second attack the tetany followed the injection of epinephrine hydrochloride. That this drug can produce tetany has been noted previously.

The entire picture is suggestive of an acute allergic reaction. Hysteria and other psychoneurotic phenomena may be safely excluded as a cause for the syndrome. In speculating on the possible specific allergic cause the acuteness of the attacks would speak in favor of extrinsic allergy. Is it possible that the patient had received any injections shortly before these attacks? Has she used a vaginal douche or contraceptive prepa-

ration, many of which could contain allergenic substances? Drugs taken by mouth should also be considered. Foods can also constitute a cause of such reactions. The proprietary vaccine should also be suspected. In addition there is some degree of possibility that internal allergens, particularly in the form of parasites such as roundworms or tapeworms, may be a cause of such allergy.

A blood calcium and phosphorus determination would be advisable. The patient should be questioned thoroughly about events, diet and so on immediately preceding the attacks. If that fails to point to a clue, cutaneous tests with likely allergens such as foods and extracts of parasites should be made. In the event that these procedures do not disclose the cause of the allergy, help may be obtained from the use of a diary by which the patient keeps record of the foods, drink and drugs ingested in order that a possible correlation with recurring attacks may be ascertained.

ASPIRATION OF BARIUM SULFATE INTO TRACHEA

To the Editor:—In the course of esophageal studies performed on a patient 70 years of age complaining of dysphagia, an esophagram taken showed reflux of barium sulfate into the trachea and bronchi. There was no evidence of esophageal abnormality nor was there evidence of a pathologic condition in the pharynx or larynx. Has regurgitation of barium into the trachea been described in an adult presenting no evidence of esophageal disease? Please quote references.

M.D., New York.

ANSWER.—Aspiration of fluids or solids into the trachea and bronchi may occur rarely in a normal person. When it does occur, it is usually during deep and sudden inspiration such as that following a cough or sneeze. The reason for the momentary and partial failure of the normal protective mechanism to function is not always clear. While it is entirely possible for barium to pass into the lower respiratory tract in a normal person accidentally, this has not been reported. Roentgenologists have occasionally noted that immediately after swallowing a barium sulfate meal a patient may gag and cough violently. When the examination is resumed, no barium is demonstrable in the trachea or bronchi. It may be assumed that in some of these cases barium entered the trachea. In this event the barium must have been expelled during the subsequent coughing spell.

If radiopaque material is found in the lower part of the respiratory tract after a barium meal it is generally considered conclusive evidence of a pathologic condition. The site of the primary disorder may be in the air or food passages, in neighboring structures or in organs which secondarily involve the air or food passages, or there may be some peripheral or central neurologic lesion which by reason of anesthesia, paralysis or incoordination interferes with the complicated series of movements and reflexes of normal deglutition. These possibilities merit serious consideration in a patient with dysphagia who has been apparently observed to have either leakage or aspiration of barium into the lower respiratory tract. The following references may be found helpful, although none mention the presence of barium in the trachea or bronchi of a normal person:

Barclay, A. E.: The Digestive Tract: A Radiological Study of Its Anatomy, Physiology and Pathology, London, Cambridge University Press, 1933.

Vinson, P. P.: The Diagnosis and Treatment of Diseases of the Esophagus, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

Jackson, Chevalier, and Jackson, Chevalier L.: Diseases of the Air and Food Passages of Foreign Body Origin, Philadelphia, W. B. Saunders Company, 1936.

COLD ALLERGY DUE TO ICE BAG

To the Editor:—A woman aged 69, who has had anginal attacks for thirteen years, was directed to apply an ice bag to her precordial area. When seen a few hours later the area was reddened as one would expect with an ice bag. The following day intense local pain developed in the skin, following which there was a diffuse coagulation of the subcutaneous tissue over the entire area in contact with the ice bag. I have heard of ice burns, but I have never seen a coagulation of tissue such as this, in which there was a hard, almost stony, feel to the tissue involved. The resolution has been extremely slow. Can you suggest a reference concerning this condition? What would be the scientific name for the pathologic condition involved?

M.D., Pennsylvania.

ANSWER.—This description seems to portray an allergic reaction. Two possibilities suggest themselves. The most likely cause would seem to be a "cold allergy." This was first described by Horton and Brown in the *American Journal of the Medical Sciences* in 1929. Horton and Roth have subsequently published articles dealing with the same subject.

The second and much less likely possibility is a sensitiveness to the material of which the ice bag was composed. It does not seem likely that the cold was severe enough to produce an "ice burn," which is actually a freezing of the skin.

URTICARIA FOLLOWING INJECTION OF BISMUTH IN PEANUT OIL

To the Editor:—A white woman aged 38 was found to have asymptomatic neurosyphilis by a recent routine serologic and spinal fluid examination. There is no history of any antisyphilitic therapy. She was given bismuth subsalicylate in peanut oil intramuscularly. Following the third weekly injection there developed a generalized urticarial eruption, which persisted until about the time of the next weekly injection. This too produced an urticaria. Treatment with this drug was discontinued, and arsenicals were started. There is no history of any allergic state; the patient never had any urticarial eruption before; she eats peanuts without any cutaneous eruption. Is it possible that her sensitivity is due to the peanut oil of the medication? Would you advise changing to a soluble bismuth compound for the next bismuth course?

M.D., New York.

ANSWER.—It is possible that the patient is sensitive to peanut oil. The information supplied is too scanty for adequate opinion. It would be advisable to get a small amount of peanut oil, sterilize it by boiling and inject a small amount and find out if she is sensitive. It is to be doubted that the urticaria is due to the bismuth itself, though it is a possibility.

Diagnosis of asymptomatic neurosyphilis suggests that the patient does not have any cardiovascular manifestations. Nevertheless she should not be put on arsenical therapy for some little time. It is better to put such a person on bismuth therapy, at least for a course of treatment. An intramuscular injection of iodobismitol 2 cc. twice a week, using the buttocks alternately and continuing this therapy for a period of ten weeks, may be tried. The patient may complain a little of discomfort from this preparation, but if the area of injection is massaged well after the injection there should be little difficulty.

If, following the injection of the iodobismitol, the urticaria returns, it would look more like a true urticarial eruption from bismuth, which is certainly rare.

WHOOPING COUGH VACCINE AND ASTHMA

To the Editor:—Several patients have asked me about the danger of asthma occurring later in life following the use of injections of pertussis vaccine. Is there any scientific basis for this belief?

C. L. Hannum, M.D., Plymouth, Ohio.

ANSWER.—Whooping cough vaccine for immunization made with human blood contains no animal protein and could neither sensitize an infant nor cause asthma later in life. For minimal local or febrile reaction, Sauer recommends the new 15,000 million per cubic centimeter Hemophilus pertussis vaccine, immunizing, prepared under the control of Northwestern University Medical School. Absorption is delayed when it is injected hypodermically in the region of the deltoid insertion. A subcutaneous lump should be visible when the needle is withdrawn. The preferred interval between the three injections is three weeks; the preferred age is the eighth month of life.

TREATMENT OF SENILE ECZEMA

To the Editor:—Is there any new treatment for senile eczema manifested by weeping and crusting of the legs on the front of the ankles and up to the knees?

K. O. Ohme, M.D., Mitchell, Neb.

ANSWER.—Wet compresses of dilute solution of aluminum subacetate, using 1 ounce of aluminum subacetate solution to the pint of cool water and applying these compresses several times daily for one hour at a time, are often of value. In the interim the use of a crude coal tar ointment is helpful. This may be made up according to the following formula:

	Gm. or Cc.
Crude coal tar	2
Solution of aluminum acetate	5
Wool fat	10
Lassar's paste to make	30

When the patient is on his feet a protective bandage, such as an Ace or Tetra bandage, should be applied. Soap and water should not be applied to the affected areas and the parts should be cleansed with a bland oil.

HEALED DEFECT IN OS CALCIS AFTER OSTEOMYELITIS

To the Editor:—A man aged 40 who had an acute hematogenous osteomyelitis of the os calcis made a full recovery, but the defect in the bone persists as shown by radiographic examination. Will this defect fill in? Can information be found in the literature? What is the experience in these cases?

M.D., North Dakota

ANSWER.—When a defect of the bone is present following an acute osteomyelitis in the os calcis of an adult, it is practically certain to persist. It may fill in somewhat, but the probabilities are that the cavity will remain.